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Review

Methods of investigation and improvement of the quality of life in oro-maxillo-facial malignancy- a systematic review

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Abstract. Objective: Cancer is a complex entity that requires a multidisciplinary approach from a team of specialists to help the patient from various perspectives. Morphological and functional impairments may be present from the beginning of the malignant process, may gradually increase or become more intense during the treatment period. Through the intervention of radioprotective agents at the molecular level it is possible to reduce the negative consequences given by the multimodal approach. The aim of the paper is to detect the radioprotective effect of amifostine administered during cancer therapy as a method of improving quality of life. Material and Method: In order to achieve the proposed goal, a systematic research of the specialized literature was carried out. Results: Favorable effects for chronic xerostomia were noted in five articles. Two papers concluded a positive outcome for acute xerostomia. Three articles did not show encouraging results on this acute symptom. Some authors have suggested that amifostine has a protective effect for other symptoms. The studies presented heterogeneous conclusions regarding the protective effect of amifostine on the tissues of the oro-maxillo-facial territory. Through the use of such methods as the administration of amifostine, patients are made aware of the possibility of improving their long-term lives. Conclusion: The cytoprotective role of amifostine is demonstrated by its selectivity to unmodified tissues. The benefits can be quantified in the long run and can facilitate the patient's recovery after cancer therapy, improving the quality of life.

Key Words: Head and neck cancer, xerostomia, amifostine, quality of life

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Introduction

Currently, cancer is considered to be one of the main causes responsible for an increased mortality rate. According to a global cancer statistic from 2018, there was an incidence of 354,864 (2% of all registered cancers) for oral cavity and lip cancer, and 92,887 new cases (0.5%) for oropharyngeal cancer (Bray et al 2018). Among the pathogenetic forms, squamous cell carcinoma is encountered with a frequency of 90% (Ettinger et al 2019). Patients with tumor pathology show multiple complex symptoms during treatment, which interfere with the development of activities and daily life (Barsevick et al 2010). The World Health Organization (WHO) defines quality of life as an individual's perception of his or her position in life, in a cultural context, and in a system of values in relation to his or her own goals, expectations, standards, and confrontations (Rathod et al 2013). Specialists in the medical and research field recognize a correlation between the quality of life, management and therapeutic approach of the oncology patient, respectively the elaboration of appropriate therapeutic policies and guidelines (Guyatt et al 1993). Assessing the quality of life with questionnaires can improve the quality of therapy (Vartanian et al 2017). Questionnaires are used in order to show the difference between the reality perceived by the patient or his expectations. To analyze these differences, a very detailed clinical evaluation is required, divided into several areas, such as: physical, functional, physiological, social and spiritual. Some of these tools are intended for either a single symptom or for function analysis, while others are extended to an overall assessment of the patient (Valdez et al 2018). Improving the international TNM system can help the physician establish the most appropriate therapeutic management of cancer and can provide a better prognosis for the patient (Takes et al 2010).

The most used therapeutic options today are surgery and radiotherapy. New surgical and radiological techniques have recently been introduced to improve the quality of treatments. Along with these, the use of systemic agents in curative therapy has been proposed (Argiris et al 2008). The most common symptom reported by patients treated with radiation therapy is xerostomia (Specht et al 2002). Xerostomia is described by the presence of a dry oral mucosa due to a salivary secretion of low consistency and quantitatively diminished. In this symptom the patient accuses the subjective sensation of dry mouth.

The cause of xerostomia is the reduced secretory activity of the salivary glands. According to the Radiation Therapy Oncology Group (RTOG) the presence of grade 3/4 disease has a significant functional and emotional impact (Strojan et al 2017). The property of agents to protect cells from cytotoxic reactions of radiotherapy is defining. The protection of the surrounding tissues with the help of such an agent may reduce the toxic effects or increase the radiation dose. Amifostine is an example of a class of radiation protection drugs with selectivity for unaffected cells (King et al 2020). Amifostine belongs to the class of thiophosphate organic compounds. Alkaline phosphatase quickly transforms amifostine into active metabolites after iv. administration. Amifostine actively binds to the membrane of cells unaffected by tumor pathology (Santini et al 2001), reduces tissue oxygen consumption (Warburg-type reaction) and prevents the condensation of the DNA macromolecule after exposure to free radicals (King et al 2020).

When administered to oncological patients, most of amifostine is concentrated in normal cells (King et al 2020, Santini et al 1999) up to an 100-fold higher rate. This difference is due to several conditions found in non-tumoral tissues: higher level of alkaline phosphatase, increased blood supply and a more basic pH. The working hypothesis of the present research supports the reduction of the severity of xerostomia after the administration of amifostine as a radioprotective agent in patients treated for oro-maxillo-facial malignancy. By conducting a systematic literature review, this paper seeks to investigate the possibility of a favorable effect of amifostine and other symptoms generated by multimodal cancer treatment. It is also intended to investigate the use in clinical trials of tools for patients to report xerostomia and other symptoms caused by the specific treatment of cancer with amifostine. The objectives pursued were: (a) monitoring of acute xerostomia in relation to the period of radiotherapy; (b) the analysis of chronic xerostomia at the follow-up consultations; (c) detection and evaluation in time of other acute and chronic symptoms; (d) mention of side effects after amifostine administration; (e) reporting the symptoms generated by the multimodal approach through specific methods dedicated to patients.

Material and method

In this research a systematic review was conducted. The study methodology was based on the PRISMA-P 2015 Checklist algorithm for systematic reviews and meta-analyzes (Shamseer et al 2015). Two databases were used in this research: PubMed.gov and Cochrane Library.com. The terms used to search for the studies were: "head and neck cancer" AND "amifostine" AND "xerostomia". For the first database, the "clinical trials" and "randomized controlled trials" filters were applied. No filter was applied regarding the date and year of publication of the articles. The studies selected from both databases were only those in the form of randomized clinical trials. The application of both filter options was performed to avoid omitting studies in the search process. Duplicate copies were removed after the total number of studies was found. Next, a screening process was performed by reading the title and abstract of each research. At this stage, studies without a connection with the topic of this research and those investigating other pathology were eliminated. Articles that did not provide the necessary information from the title or abstract were searched in full format and researched in detail. In the following stage, the eligibility criteria of the studies were applied, as listed below:

(1). Availability of the text in full format;
(2). Clinical trial or randomized controlled trial;
(3). Adult patients (> 18 years of age) with oro-maxillo-facial and cervical malignancy;
(4). Allocation of treatment specific to malignant pathology, without other additional interventions;
(5). Addressability of the research topic (relationship oncology therapy - amifostine administration - xerostomia);
(6). Experiment-control or experiment-placebo design;
(7). Mention of results in the form of quantitative data;
(8). Article written in English;
(9). Respecting the structure of IMRAD (introduction, material and method, results, discussions).

Each item that did not meet at least one of the stated criteria was excluded from the analysis. Qualitative evaluation of individual studies was performed with Oxford Quality Scoring System (Jadad et al 1996) available online.

Possible publishing errors were analyzed through the online application robvis, the RoB 2.0 option for randomized clinical trials (McGuinness and Higgins 2020). Based on an Excel file provided by the application, the data corresponding to each study were completed.

Regarding the "Final Assessment", an average was made according to all the evaluated areas. For the variable "Quantitative assessment of the effect of the intervention" was used the percentage of patients exposed to amifostine who developed acute xerostomia of grade ≥ 2. For studies that used several groups exposed to the intervention, an arithmetic mean of the reported effect was performed. For studies that did not provide quantitative data on acute xerostomia, the application recommendation was used and assigned a value of 1. The completed database was uploaded online, and the results in the form of graphs were generated automatically. The results of the described objectives were transformed into tables and figures using the Excel program.

Results

A total of 86 articles were generated as a result of the search process. 37 duplicate copies were identified and removed. The studies that went through the screening stage of the title and the abstract were 49 in number. Following the screening process, 6 articles were removed from the analysis. The eligibility criteria were applied for the 43 articles. A total of 36 articles did not meet at least one of the criteria and was removed from the research. The final number of studies included in the review was 7 articles (Figure 1).

The publication period of the 7 articles considered eligible was between 2000-2019. All selected studies were of the randomized clinical trial type. Of the total articles, five used a control group to compare the results, and two used placebos (one of them had a volumetric equivalent of mannitol, and the second used 0.9% saline).

Two of the studies had the double-blind method in the research project.

The research was conducted for two of the seven studies in several medical institutions. Four articles mentioned the research

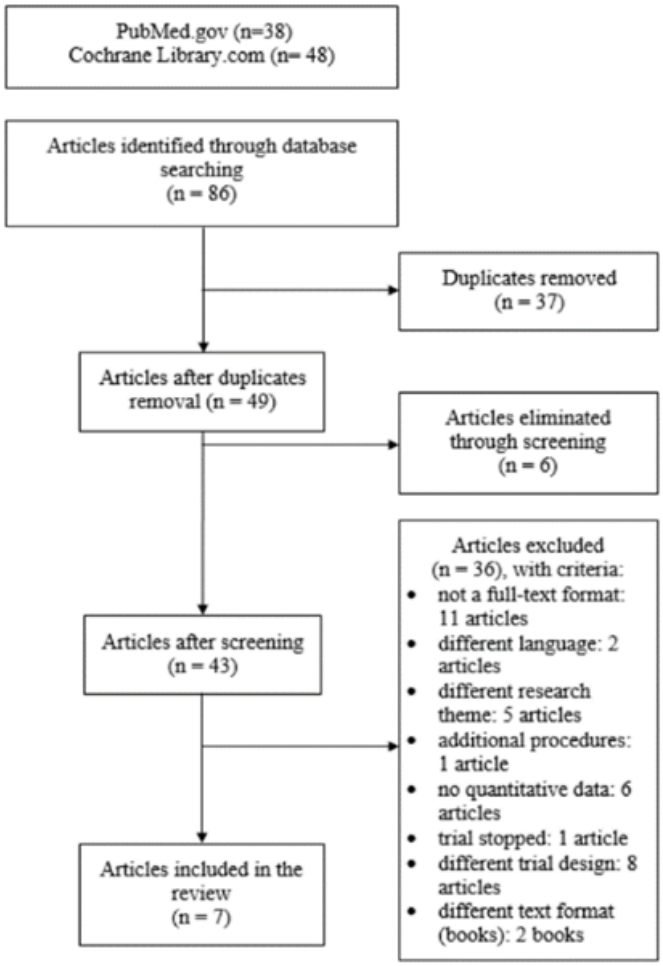

Figure 1. The flow chart for the eligible studies, based on the PRISMA model (Moher et al 2009)

phase (two studies in phase II and two in phase III). Two studies looked at collecting data from patients as a prospective way (Jellema et al 2006, Vacha et al 2003). One study presented a control group and two experimental groups, administering amifostine with different frequencies. One study out of seven presented three randomized clinical trials in a single article. Two of the trials presented were not considered eligible according to the inclusion criteria. One trial met all the criteria and was included in the analysis. The patient recruitment period for the study was 1995 (Table 1).

The localizations of the tumors were reported for the amifostine group. The highest percentage was attributed to oropharyngeal cancers (56%), followed by oral cancer (22%). The study by Jellema et al presents for the first experimental group the pathology of the oropharynx with the highest frequency. The second experimental group more frequently presented the malignant tumor with a starting point in the oral cavity. One study (Lee et al 2019) reported an equal percentage of locations among patients treated with amifostine (oropharynx and supraglottic larynx). The article written by Büntzel et al (2002) specifies the enrollment of an additional number of patients in the experimental group. Out of a total of seven articles, only six specified the diagnosis of squamous cell carcinoma as an inclusion criterion.

The selected articles included in the protocol the staging of TNM regarding the location of the primary tumor and the lymph node status of the patients. All subjects in the study were over 18 years of age. Recruitment periods in the study and treatment were variable for each article.

Multimodal approach

All included studies presented a multimodal approach to cancer. The study of Buentzel and collaborators specified the characters of the margins following the surgery. The last two included studies present the postresective status (complete, incomplete or inoperable status - Lee et al 2019, Vacha et al 2003) and the possibilities of performing lymph node dissection (unilateral, bilateral or inoperable - Vacha et al 2003).

The seven researches used radiotherapy to treat patients. In four cases they mentioned the radiotherapy technique with curative intent. Four studies used additional doses of radiation (boost) after evaluating surgical procedures. One study did not use surgical procedures on patients (Antonadou et al 2002). Five articles support the use of adjuvant radiotherapy, after evaluating the resection margins. Five studies described chemotherapy in the patients' therapeutic protocol, but only four of them specified the cytostatic agent used (carboplatin). Chemotherapy was performed concomitantly with radiotherapy sessions for five studies out of a total of seven (Table 2).

Amifostine administration protocol

Amifostine was administered by the same route (intravenously) for all research. The time it was administered was before the radiotherapy sessions (five studies) or before the chemotherapy sessions (two studies). The article by Buentzel and colleagues (2006) administered amifostine in different doses throughout the multimodal treatment. Only one article presented the results of the two groups exposed to amifostine (Jellema et al 2006).

During cancer treatment, the use of interventions to alleviate the resulting toxic effects has been reported. Six articles mentioned the use of an appropriate hydration regimen, along with antiemetics during radio or chemotherapy (Antonadou et al 2002, Buentzel et al 2006, Büntzel et al 2002, Brizel et al 2000, Jellema et al 2006, Lee et al 2019), 8 mg ondansetron (Büntzel et al 2002, Lee et al 2019) and 5 mg tropisetron were specified from the range of antiemetics (Lee et al 2019), hydroxytryptamine antagonists (Büntzel et al 2002), phenothiazine and metoclopramide (Brizel et al 2000). The use of dexamethasone was mentioned in the articles of Antonadou et al (2002) and Büntzel et al (2002) to reduce side effects. Pilocarpine for prophylactic purposes was not accepted in two studies (Brizel et al 2000 and Lee et al 2019). For both studies, the use of pilocarpine was a criterion for excluding patients (Table 3).

Assessing acute xerostomia

Out of a total of seven eligible studies, only five investigated the occurrence of acute xerostomia. The articles of Antonadou et al (2002) and Büntzel et al (2002) did not aim to evaluate this symptom during treatment or during the related period. All studies that included the reporting of acute xerostomia had variable intervals for radiation therapy and analysis. The study by Buentzel et al (2006) further investigated patients who suffered from acute xerostomia for another 6 and a half weeks after treatment completion. It was considered that in this interval the patients were still in an acute state. The second article (Brizel et al 2000) that dealt with xerostomia reported a six-week period

Table 1. Data extraction for the eligible research

First author	Year	Publication	Study type	Study design
Antonadou D et al	2002	Int J Radiat Oncol Biol Phys	Randomized controlled clinical trial	Exposure - control
Buentzel J et al	2006	Int J Radiat Oncol Biol Phys	Multicenter double-blind randomized clinical trial, phase III	Exposure - placebo (volumetric equivalent of mannitol)
Büntzel J et al - recruitment period: 1995	2002	Semin Radiat Oncol	Randomized clinical trial, phase II	Exposure - control
Brizel DM et al	2000	J Clin Oncol.	Open controlled, multi-institutional randomized clinical trial, phase III	Exposure - control
Jellema AP et al	2006	J Clin Oncol	Prospective randomized clinical trial, phase II	2 groups exposure – 1 group control
Lee MG et al	2019	J Med Imaging Radiat Oncol	Double blind randomized clinical trial	Exposure - placebo (saline conc. 0.9%)
Vacha P et al	2003	Strahlenther Onkol	Prospective controlled randomized clinical trial	Exposure - control

Table 2. The multimodal approach used in the selected trials

First author	Treatment methodology
Antonadou D et al	Chemoradiotherapy: conventional fractional curative radiotherapy Comprehensive dose (boost) or electron beam at the end of radiotherapy + carboplatin 90 mg / m^2
Buentzel J et al	Surgical resection Chemoradiotherapy: standard radiotherapy fractionated with the isocentric external beam + carboplatin 70 mg / m^2
Büntzel Jet al - recruitment period: 1995	Microsurgical resection with laser Functional or radically altered lymph node dissection Chemoradiotherapy: fractional radiotherapy + carboplatin 70 mg / m2
Brizel DM et al	Surgical resection Lymph node dissection Definitive or postoperative radiotherapy fractionated with the isocentric external beam
Jellema AP et al	Surgical resection Fractional primary or postoperative radiotherapy Additional doses for boost negative margins and for extracapsular invasion or positive negative margins
Lee MG et al	Surgical resection Chemoradiotherapy: conventional fractional radiotherapy Optional extra dose
Vacha P et al	Surgical resection Radical, selective or selective supraomohyoid ganglion hollow Chemoradiotherapy: conventional fractional radiotherapy + carboplatin 70 mg/m^2 Additional dose (boost) for R 1-2 resective margins

for radiation therapy. A thirteen-week assessment of the symptom was required. Patients in the third study (Jellema et al 2006) underwent radiotherapy for five weeks. Acute xerostomia was monitored for another seven weeks after the end of treatment. In the fourth article (Lee et al 2019), the therapeutic approach was carried out for six and a half weeks, and the xerostomia was analyzed until the twelfth week after the start of treatment. For the latest research (Vacha et al 2006) the arithmetic mean of the treatment weeks was made due to the different doses of radiation administered (6 weeks and 7 weeks). Acute xerostomia in this research was analyzed for six weeks.

Chronic xerostomia evaluation

After the end of the multimodal treatment, the incidence of chronic xerostomia was mentioned in six articles. Antonadou et al (2002) and Buentzel et al (2006) reported the severity of this symptom starting with the third month after the end of therapy. Two studies mentioned the presence of xerostomia at

Table 3. The administration protocol of amifostine used in research

First author	Amifostine regimen
Antonadou D et al	One dose of 300 mg/m^2 i.v within 30 minutes before radiotherapy on days 1-5, for six-seven weeks and a half
Buentzel J et al	One dose of 300 mg / m^2 i.v slowly for 3 minutes before chemotherapy, on days 1-5 and 21-25 One dose of 200 mg/m^2 i.v slowly for 3 minute before radiotherapy, on days 6-20 and 26-30/35
Büntzel J et al - recruitment period: 1995	One dose of 500 mg/m^2 i.v before chemoradiotherapy on days 1-5 and 29-34
Brizel DM et al	One dose of 200 mg/m^2 per day prepared with saline of concentration 1 mg/ml i.v for 3 minutes before radiotherapy
Jellema AP et al	(1): One dose of 200 mg/m^2 prepared with 0,9% saline, for three times per week, before radiotherapy (2): One dose of 200 mg/m^2 prepared with 0,9% saline, for five times per week, before radiotherapy
Lee MG et al	One dose of 200 mg/m^2 i.v slowly for 3 minutes before radiotherapy
Vacha P et al	One dose of 250 mg/m^2 i.v slowly for 10-15 minute before radiotherapy

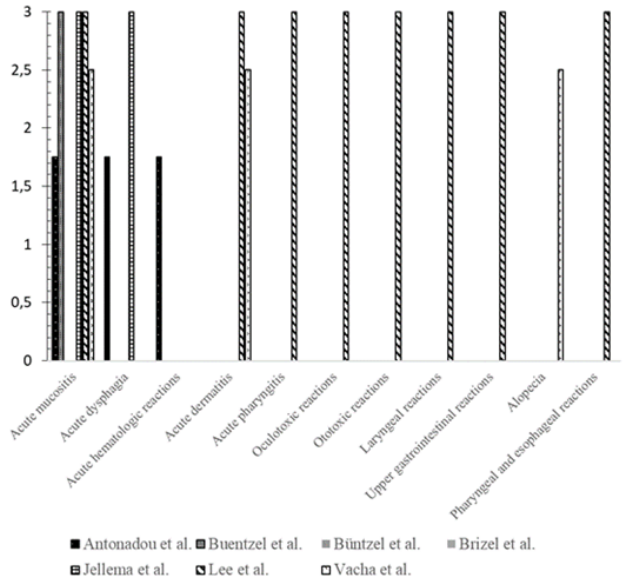

Figure 2. Acute symptoms monitoring time frame (months)

the six-month post-therapeutic consultation (Antonadou et al 2002, Jellema et al 2006). Six articles investigated the severity of chronic xerostomia one year after completion of cancer therapy (Antonadou et al 2002, Buentzel et al 2006, Büntzel et al 2002, Brizel et al 2000, Jellema et al 2006, Lee et al 2019). One article did not investigate chronic xerostomia among patients (Vacha et al 2003). Criteria for the analysis of xerostomia and symptoms caused by oncological treatment were quantified according to RTOG guidelines. Particularly for xerostomia, measurement scales with values between 0 and 4 were used. All included studies used the RTOG system, applying the specificity of the irradiation period (acute or chronic) to estimate the acute or chronic symptoms.

Acute symptoms analysis

Five articles were identified that investigated acute changes during treatment. Antonadou and colleagues monitored for about two months the severity of acute mucositis, dysphagia, and blood pressure. Buentzel et al (2006) reported cases of acute mucositis during the three months. The third study (Jellema et al 2006) investigated the severity of dysphagia and mucositis over a three-month period. The article by Lee et al (2019) reported the presence of acute dermatitis, oculotoxic, ototoxic reactions, toxic effects in the pharynx, larynx, esophagus, upper digestive tract, pharyngitis and acute mucositis during the three months of treatment. The last study (Vacha et al 2003) presented cases of alopecia, mucositis and acute dermatitis during two and a half months of therapy. Two articles (Büntzel et al 2002 and Brizel et al 2000) did not investigate acute symptoms present among patients during multimodal treatment (Figure 2).

Follow-up consultation for chronic symptoms

Patients were evaluated at regular check-ups for certain chronic symptoms. Of these, mucositis, dysphagia and chronic dermatitis were reported to a greater extent. Four studies (Antonadou et al 2002, Büntzel et al 2002, Brizel et al 2000, Lee et al 2019) specified the description of symptoms with a long evolution after the end of treatment.

Questionnaires for outcome quantification

The studies of Brizel et al (2002), Jellema et al (2006) and Lee et al (2019) used questionnaires as tools for patients to report symptoms. The first article used the Patient Benefit Questionnaire (PBQ), which presents 8 questions with answers in the form of a 10-point scale. The questionnaire was given to patients before, during treatment and at each follow-up consultation. The areas analyzed were: xerostomia, phonation, taste sensation, swallowing, the need for oral medication for comfort.

The second study (Jellema et al 2006) benefited from the EORTC QLQ-C30 questionnaire, intended for general health, and the EORTC QLQ-H&N35, specific to the oro-maxillo-facial symptoms. Participants answered questions before starting treatment, in the sixth week of therapy, 6 to 24 months after the end of

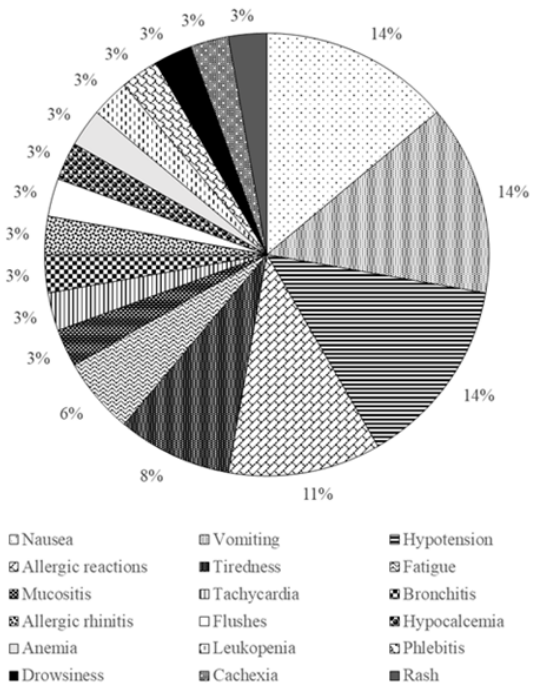

Figure 3. Adverse effects after exposure to amifostine

radiotherapy. The questionnaires included questions on: xerostomia, salivary consistency, other specific oro-maxillo-facial and cervical symptoms. Response options were formulated in the form of scales 1 to 4 (no symptoms, minimal symptomatology, moderate symptomatology, or severe symptomatology). The last article (Lee et al 2019) presented the EORTC QLQ-H&N35 module in the pre- and post-treatment period.

Adverse side effects

With the exception of one study, all studies reported the presence of side effects after amifostine. The article by Vacha et al. did not show the presence of significant toxic reactions. Three studies monitored the blood pressure before, during and shortly after the intravenous infusion of the drug (Antonadou et al 2002, Jellema et al 2006, Vacha et al 2003). The exposed group was also maintained in the supine position during the administration procedure (Buentzel et al 2006 and Jellema et al 2006). Toxic reactions were evaluated according to the criteria of the National Cancer Institute Common Toxicity Criterion version 2.0 (NCI CTC v2.0). The evaluation method was described only in three studies (Buentzel et al 2006, Brizel et al 2000, Lee et al 2019). The most common side effects reported in all studies were hypotension, nausea and vomiting (14%). Allergic reactions (11%), asthenia (8%) and febrile reactions (6%) were reported in a lower percentage. Most adverse reactions were reported in a minimal percentage. For studies that used the multimodal approach through surgery and radiation therapy, nausea was the most common side effect among exposed patients. In patients treated with chemoradiotherapy, the most significant side effects from amifostine were hypotension and asthenia (Figure 3).

The radioprotective quality of amifostine

The studies present heterogeneous conclusions regarding the protective effect of amifostine on the tissues of the oro-maxillo-facial territory.

Table 4. Quality scoring and interpretation, based on Oxford Quality Scoring System (Jadad et al 1996)

First author	Score and interpretation
Antonadou D et al	2 = low score
Buentzel J et al	3 = high score
Büntzel J et al	-1 = low score
Brizel DM et al	2 = low score
Jellema AP et al	2 = low score
Lee MG et al	5 = high score
Vacha P et al	0 = low score

Two of the seven studies tested positive for acute xerostomia (Brizel et al 2000, Vacha et al 2003). Three articles did not show encouraging results on this symptom (Buentzel et al 2006, Jellema et al 2006, Lee et al 2019). Favorable effects for chronic xerostomia were noted in five articles (Antonadou et al 2002, Büntzel et al 2002, Brizel et al 2000, Jellema et al 2006, Lee et al 2019). Research by Buentzel and colleagues (2006) has shown that amifostine is ineffective in chronic xerostomia. Regarding administration frequencies, the study by Jellema (2006) did not show a statistically significant difference for the two exposed groups and the severity of xerostomia.

Some authors have suggested that amifostine has a protective effect for other symptoms. Acute mucositis was ameliorated in the research of Antonadou and collaborators (2002), respectively Vacha and collaborators (2003). On the other hand, two articles noted that oral mucositis did not decrease in patients treated with amifostine during treatment (Buentzel et al 2006, Lee et al 2019), while another study found no significant differences (Jellema and al 2006). An improvement in acute dysphagia was observed in the research of Antonadou et al (2002). The results were not statistically significant for research on acute dysphagia (Jellema et al 2006). Results on acute dermatitis were negative for one study (Lee et al 2019) or no differences were observed between groups in another study (Vacha et al 2003).

Chronic mucositis was ameliorated by amifostine in two studies (Antonadou et al 2002, Büntzel et al 2002). Another author did not notice improvements in chronic mucositis (Brizel et al 2000). Chronic dysphagia was lower in intensity for two trials (Antonadou et al 2002 and Büntzel et al 2002), and chronic dermatitis decreased after administration of the drug in two articles (Büntzel et al 2002, Lee et al 2019). However, the study by Lee et al (2019) reports some more serious toxic effects for patients who have been given the substance compared to the placebo group. Buentzel et al (2006) however, demonstrates the safety of use in clinical trials. Büntzel and colleagues (2002) attest the protective role of amifostine against the toxic effects of the treatments applied. Their research also denies the interference of amifostine with the multimodal treatment of malignant pathology. The trial of Brizel and co-workers (2000) claims a higher survival rate for patients receiving amifostine, but this hypothesis has not been statistically proven.

Quality appraisal and risk of bias

The article with the highest degree of quality was the one written by Lee et al (2019), followed by Buentzel et al (2006). Only

one study showed a negative score. The ratio of high quality versus low quality studies was 2 to 5 (Table 4).
The overall analysis of all articles concluded the following: the lowest risk of bias was attributed to the correctiveness of the randomization process and the way of presenting the results obtained. In a higher percentage, the errors regarding the pursuit of the established goal and objectives were evaluated, respectively the amount of omitted information. The highest percentage was obtained for errors given by the investigation and reporting of results.
Four studies out of seven had a lower exposure to publication errors. For three items the risk of bias was significantly higher. The most affected areas were those related to the reporting of the results obtained from the exposure of patients to the administered substance (two studies).

Discussion

It can be stated that the present research has achieved its intended purpose. The working hypothesis could be confirmed: amifostine reduced the severity of xerostomia when administered before radiotherapy or chemotherapy.
In particular, there were five studies that concluded a reduction in this chronic symptom (Antonadou et al 2002, Büntzel et al 2002, Brizel et al 2000, Jellema et al 2006 and Lee et al 2019). One study, on the other hand, denied the reduction of chronic xerostomia after amifostine administration (Buentzel et al 2006). The literature (Holmberg et al 2014) provides the same encouraging clarification regarding chronic xerostomia. However, there are a number of differences in the studies included (the use of surgical procedures and total radiation dose). Two other studies have had encouraging results on chronic xerostomia, but only applying in case of fractionated radiotherapy (Brizel et al 2000, Jellema et al 2006). The papers present some similarities: both performing surgical procedures and using fractionated radiation doses.
Investigation of amifostine with agents that could reduce the fibrosis of salivary glands may be a way to slow the degeneration of the structures.
Favorable results on acute xerostomia were obtained in two articles out of seven (Brizel et al 2000, Vacha et al 2003). The articles addressed different therapeutic strategies. Brizel and collaborators (2000) used surgery and conventional fractionated isocentric external beam radiotherapy. Vacha's study and collaborators (2003) used surgical procedures, conventional fractional radiotherapy, and carboplatin-based chemotherapy. The analyzed studies brought different conclusions regarding the amelioration of acute xerostomia. Buentzel and colleagues (2006) proposed, together with data from the literature (Cassatt et al 2003, Peters et al 1999), the issue of dosage and when amifostine was administered. Still, it appears that a dose of 200 mg / m2 is sufficient to ameliorate acute and chronic xerostomia but is not effective against acute mucositis. For increased protection, higher doses of 300 mg / m2 are recommended. (Brizel et al 2000).
The American Society of Clinical Oncology (ASCO) guidelines recommend daily use of amifostine 200 mg / m2 slowly intravenously for 3 to 30 minutes before radiation therapy (Kouvaris et al 2007). The present study proposes the investigation in order to improve acute xerostomia the administration of amifostine in the period preceding radiotherapy. According to data from the literature (Harris et al 2018), a shorter time interval from the end of surgery to the start of radiotherapy sessions can improve the survival rate of patients. Specialists believe that a delay of 50 days from the completion of surgery brings an unfavorable prognosis. By reducing the time frame for starting radiotherapy and administering amifostine in this preoperative period, it is possible to decrease the severity of acute xerostomia and achieve a better survival rate.
The use of amifostine along with different radiation techniques and personalized irradiation fields can help to save the salivary glands and keep the function in the right parameters. Subsequent research may focus on comparing efficacy between amifostine and other cytostatic or immunomodulatory agents, such as cisplatin, 5-fluoruracil, or cetuximab (exposure-control trials). In the case of chemotherapy, the literature mentions a dose of 910 mg / m2 of amifostine administered intravenously 15 minutes before cancer therapy. However, there is no consensus regarding the maximum allowable dose, so in clinical trials doses up to 2,700 mg / m2 were used. (King et al 2020, Adamson et al 1995). The purpose of future research may determine the possibility of a more favorable effect of the preparation and amelioration of toxic effects or on the contrary, the increase of adverse reactions.
Other researchers have evaluated the effectiveness of other routes of administration. Anné and colleagues (2007) investigated subcutaneous administration in a group of patients treated with fractionated radiotherapy. Patients in the early stages of the pathology may have functional swallowing. The development of oral preparations facilitates the administration of amifostine to this category of patients and avoids a number of disadvantages of intravenous route (avoidance of venous puncture, reduction of accidents and complications after catheter insertion, decrease patient anxiety, reduce costs and materials). Oral preparations have other advantages: the patient can be instructed to self-administer or can be helped by a relative. Several studies on the contribution of amifostine to the reduction of other acute and chronic symptoms are needed. The most common acute symptoms analyzed were: mucositis (5 articles), dysphagia (2 articles) and dermatitis (2 articles). Two trials (Antonadou et al 2002 and Vacha et al 2003) obtained a reduction in the severity of acute mucositis. Buentzel and colleagues (2006) found a higher incidence of acute mucositis in patients treated with amifostine, and Jellema found no differences in the experimental and control groups. Acute dysphagia, monitored in two studies, drew different conclusions. The first study observed an improvement in symptoms after amifostine (Antonadou et al 2002), while the second study did not observe significant differences (Jellema et al 2006). Acute dermatitis has been followed in Lee et al (2019) and Vacha's et al (2003) research. Lee and colleagues found worsening of dermatitis after amifostine, while Vacha and colleagues found no differences between the exposed and control groups.
The most commonly followed chronic symptoms were: mucositis (3 studies), dermatitis (2 studies) and dysphagia (2 studies). Chronic mucositis was ameliorated in patients receiving amifostine in two studies (Antonadou et al 2002 and Büntzel et al 2002). The third study (Brizel et al 2000) did not notice an improvement for the experimental group. Encouraging results

have been obtained for chronic dysphagia (Antonadou et al 2002 and Büntzel et al 2002). Chronic dermatitis was investigated in two articles (Büntzel et al 2002 and Lee et al 2019) and decreased in intensity after amifostine. However, the results cannot clearly support the protective role of amifostine against these toxic reactions.

Investigating methods to improve xerostomia can avoid the installation of other toxic reactions or complications given by the multimodal approach. Xerostomia can be a favorable factor for the installation of other complications, such as oral mucositis or feeding difficulties. Nicolatou-Galitis's study exposes the problem of xerostomia and the favorable ground for the development of oral candidiasis (Nicolatou-Galitis et al 2003).

It is necessary that the preparation does not interfere with the multimodal treatment chosen for malignant pathology. The use of amifostine should be justified to improve symptoms, according to Brizel et al (2000). Another aspect to consider is the possible side effects of amifostine. The occurrence of side effects requires collaboration with specialists (cardiologist, allergist) for their management and avoid the installation of complications. The crawling organism can be overworked after oncological therapy, and any negative effect can have a significant impact on quality of life. Recourse to an increased number of treatments and specialists can cause anxiety or depression among patients with malignant pathology. This paper presents similar results to other studies in the literature. Rades' paper (Rades et al 2004) mentions the same side effects seen in patients after amifostine. Thus, the study states that hypotension was the most common symptom, followed by nausea and allergic manifestations.

Eisbruch's review study (2011) analyzes administration variants. The author presents the tendency of specialized studies to choose the subcutaneous route, as it seems to have certain advantages, such as the low degree of difficulty and the lack of need for continuous monitoring of blood pressure. Contrary to this view, Bardet and colleagues (2011) conducted a clinical trial that demonstrated the benefits of the intravenous route. The extent of toxic effects and side effects is often difficult for the doctor to assess. Questionnaires prepared by the specialized commissions can help the patient from several points of view, such as: understanding the diagnosis, symptoms and possible complications that may occur during treatment, support and strengthen the relationship with loved ones, facilitate communication with the doctor and improve compliance compared to the proposed therapy. The symptoms that occur are vast and depend on the chosen multimodal approach, the time at which the treatment was performed, as well as the body's tolerance capacity. At present, there is no standard time to apply the questionnaires. The most used questionnaire was the EORTC QLQ-H&N35 module. Jellema and co-workers (2006) mention as a disadvantage that this tool only presents a question about the severity of xerostomia. This makes it difficult to analyze the symptom, bringing incomplete information. The preparation of questionnaires that address specific symptoms can provide complete data on severity.

Such a questionnaire was developed by Lastrucci and his collaborators (2018) for xerostomia. The XeQoLS questionnaire (The Xerostomia Quality of Life Scale) was applied to patients with oro-maxillo-facial malignancy, treated with radiotherapy.

The present study presents certain limitations that should be mentioned. First, the use of a small number of databases and the inclusion of studies only in English. Also, the method of reporting the results regarding the radioprotective effect showed significant differences between studies. The omission of information in articles is another limitation of this paper. The quality of research is significantly influenced by possible mistakes made in clinical trials. The different methodology applied, the moment of analysis of the xerostomia, the acute and chronic symptoms as well as the way of administering amifostine represent other differences noticed in the studies. However, the authors' contributions represent an important step in investigating methods of improving the quality of life for patients with oro-maxillo-facial malignancy.

Conclusion

The application of multimodal treatment protocols to this category of patients is the standard of oncological therapy. The ultimate goal is to heal, survive and obtain a favorable long-term prognosis. The development of radiotherapy techniques is one of the directions of research in the medical field. The design of methods to combat malignant tumors with the help of modulated radiation or the use of selective irradiation fields can significantly improve the prognosis and quality of life. However, administration of amifostine may be another method of ameliorating symptoms. The research brings a new perspective on the role of chemical agents in cancer therapy. Future clinical trials may develop this field of radiation protection agents and may investigate new solutions for the prophylaxis of toxic reactions. The decision to use amifostine should weight the potential benefits and risks to which the patient will be exposed from the time the diagnosis is made. Any gesture can have unwanted repercussions or, on the contrary, can increase the quality of life.

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