VIA MEDICA

Review article

NOWOTWORY Journal of Oncology
2020, volume 70, number 6, 253–259
DOI: 10.5603/NJO.2020.0049

ISSN 0029–540X
www.nowotwory.edu.pl

# Oral mucositis (OM) – a common problem for oncologists and dentists

Magdalena Stawarz-Janeczek, Katarzyna Szczeklik, Jolanta Pytko-Polończyk

*Department of Integrated Dentistry, Institute of Dentistry, Jagiellonian University Medical College, Krakow, Poland*

Oral mucositis (OM) caused by ionizing radiation is a significant therapeutic problem concerning almost all patients with head and neck cancers undergoing irradiation, however, an effective treatment method is still missing. Therapeutic actions concentrate mostly on prophylaxis, including the maintenance of the correct hygiene of the oral cavity. In 2014 the International Society of Oral Oncology (ISOO) together with the (Multinational Association of Supportive Care in Cancer (MASCC) worked out the guidelines for the treatment of patients with z OM induced by radiotherapy and chemotherapy. In 2019 these guidelines were updated.

Research is ongoing to find medication which could be applicable for the prevention and treatment of OM. The problem is grave as it might complicate the progress of oncological treatment, deteriorate the patient's quality of life or even affect the prognosis.

This paper describes the pathogenesis of oral mucositis, the current trends in treatment and discusses the role of a dentistry doctors in the care of the patient with symptoms of this condition. The article also refers to the role of a multidisciplinary team – the OM prophylaxis – as part of the preparation of an oncological patient for irradiation.

**Key words:** oral mucositis, prophylaxis, oral hygiene, radiotherapy, chemotherapy, head and neck cancers

## Introduction

Unaffected oral mucosa makes up the best protection against pathogens and other external factors. In the majority of patients, the lesions of the oral mucosa – irrespective of their origin – cause significant discomfort, as they are usually accompanied by pain and difficulties in chewing and swallowing. In recent years, on account of the growing number of patients receiving the anti-cancer treatment and due to their prolonged duration of life, the number of patients contacting dentists due to various complains about the condition of oral mucosa caused by complications arising from oncological treatment has increased.

Malignant cancers are one of the main causes of death in Poland and worldwide. According to the National Cancer Register, the incidence of malignant tumours in Poland, in the last 30 years has doubled, whilst the number of deaths within the last 50 years has increased 2.4-fold. [1]. Cancers located in the area of the head and neck account for between 5.5% and 6.2% of all malignant cancers in Poland. Other European countries and the United States have noted similar prevalence rates [2]. The basic methods of treatment in the case of this type of cancer comprise surgery and radiotherapy – often combined with systemic treatment. However, the use of irradiation is connected with the risk of development of oral mucositis (OM), which might be exacerbated in patients undergoing chemotherapy together with radiotherapy. OM is induced by ionising irradiation and is regarded as one of post-radiation acute reactions. It concerns almost all patients undergoing chemotherapy in the area of the head and neck [4, 5, 7–10 ]. Such a reaction was described for the first time

**How to cite:**
Stawarz-Janeczek M, Szczeklik K, Pytko-Polończyk J. ***Oral mucositis (OM) – a common problem for oncologists and dentists.*** *NOWOTWORY J Oncol* 2020; 70: 253–259.

in 1980 in patients with head and neck cancers undergoing radiotherapy [5, 6]. In 2007 the World Health Organization (WHO) considered oral mucositis as a separate disease unit [3, 4].

## Patomechanism

OM is caused by mechanisms which directly and indirectly affect the cells of the oral epithelium, including their division and maturation [5]. The direct impact of irradiation is connected with apoptosis induction [5, 11]. Indirect mechanisms consist in the release of proinflammatory mediators with simultaneous reduction of the release of anti-inflammatory mediators in the cells of the oral epithelium [5]. Sonis worked out the five-stage model of OM development induced by radio- and chemotherapy [3]. In the first stage, called the **initiation stage**, direct DNA damage occurs and reactive oxygen species (ROS) are released. [3, 12, 13]. The second stage is called **signalling**: in this stage transcription factors, such as NF-kB, are activated. As a result of complex biological processes, the number of proinflammatory cytokines – such as TNF-α, IL-1-β, IL-6 – increases [3, 5, 14], whereas, at the same time, the number of anti-inflammatory cytokines, such as IL-10 and TGF-β decreases [3, 14]. As a result of the expression of more than 200 various genes, the molecules responsible for epithelial damage and the activation of other molecular pathways are produced [3]. It must be emphasised that the NF-kB protein complex plays a main role in the development of radiotherapy induced OM. OM may develop directly under the influence of chemotherapy or radiotherapy, and indirectly – by ROS [3, 6, 12]. The effect of the activation of this pathway may be programmed cell death by means of apoptosis [3]. The third stage of OM development is **amplification**, i.e. m signal magnification. At this point the inflammatory cascade is activated. The clinical manifestation is comprised of oedema and erythema caused by the activation of proinflammatory cytokines [3]. The fourth phase – **ulceration** – is regarded as the most significant with respect to its clinical picture [3]. The rapid development of biological processes leads to the apoptosis of the epithelial cells. Deep, clinically overt ulceration develops and this might easily be colonised by pathogens. Bacteria cause mucositis, whilst the products of the lysis of the cellular walls penetrate to the submucosal membrane, increasing the proinflammatory effect. After the penetration of living bacteria into the blood vessels in the submucosal layer of the mucosal membrane, inflammation might develop into a systemic infection (sepsis). The risk of sepsis, originating in the oral cavity is especially present in patients with additional risk factors, such as granulocytopenia induced by anti-cancer treatment [6, 12]. The fifth phase of the OM evolution patomechanism is **healing** [12]. The majority of cases of oral mucositis, thanks to biological reparatory pathways, are spontaneously healed [3].

## Risk factors and location of the lesions

There are risk factors which predispose the development of OM: their analysis facilitates taking preventive steps and the definition of therapeutic goals [3]. The OM risk factors comprise:

- poor hygiene status of the oral cavity,
- the presence of defects caused by dental caries,
- lesions of the oral mucosa,
- tobacco smoking,
- poor nutritional status,
- systemic comorbidities (e.g. neutropenia),
- folic acid and B12 vitamin deficit,
- oral cavity dryness,
- some medication (e.g. cytotoxic drugs with muco-toxic action),
- age (the risk is higher before 20 and after 50 years of age),
- sex (OM is more frequent in women),
- genetic factors (np. *MTHFR C677T* nucleotide polymorphism in patients treated with methotrexate) [5, 9, 10].

Lesions connected with OM are located mainly in the movable, non-keratinising mucosa. They affect mostly the buccal mucosa, the inside surface of the lips, the lateral and ventral side of the tongue, the fundus of the oral cavity, soft palate and pharynx mucosa [3, 7, 15, 16].

## The course of the disease

The one of the main symptom of OM is a burning sensation in the oral cavity. Ulceration is deeper than in the case of *aphthous stomatitis* and makes a gateway for bacterial infection (Gram+ and Gram–) infections. Opportunistic infections (OIs) may hinder diagnosis and treatment [3, 11, 15]. Within the course of oral mucositis, the probability of infections increases – not only of bacterial origin, but also mycotic or viral [11, 17]. The infections are also stimulated by decreased saliva production caused by the anti-cancer treatment (damage of salivary glands) and neutropenia [3, 5, 9, 18].

In patients suffering from head and neck cancers, the lesions induced by OM may vary with regards to their intensity, depending, among others on the irradiation dose and its possible combination with chemotherapy [9, 11].

Oral mucositis may lead not only to difficulties in food consumption, but also in everyday life [19]. The immunity of these patients is compromised, and thus the risk of developing other diseases, also in the oral region, is greater [15]. Loss of body weight or emaciation of the whole organism as well as resulting outcomes such as sepsis and death are likely [12]. The total duration of treatment and hospital stay are longer, more medication is required, and the patient needs interventions in hospital more frequently [5]. Also the economic outcomes of OM are significant for the healthcare system [5, 10]. OM symptoms also impair the patient's quality of life and may lead to depression and social isolation resulting from problems with food intake and speech [5]. Moreover the quality of life is decreased and swallowing problems can occur. In such

situations it is necessary to modify the anti-cancer treatment or even completely discontinue it, which can certainly lead to rather adverse outcomes [5, 9, 10].

## Diagnosis

There are many classifications applied for the evaluation of the intensity of OM [3]. The majority of centres base their evaluation on the five-grade scale worked by the WHO [15] (tab. I).

In order to make a quick diagnosis of OM, it is necessary to make a frequent and detailed physical examination and take a detailed history of the patients undergoing radiotherapy. The time of symptom occurrence and the intensity of OM must be monitored during therapy [11].

## Prevention and treatment

So far, no effective method of OM treatment has been introduced [22], that is why a key role is played by prophylaxis [9]. The preventive actions concentrate in the improvement and maintenance of the correct oral cavity hygiene and symptomatic treatment [22]. Laser therapy and cryo-therapy play an important role. In patients undergoing chemotherapy, Bockel et al. used laser therapy 2–3 times per week with a low power laser (630–660 nm) and obtained good therapeutic effects [13]. Daugėlaitė et al., in 2019 published a metanalysis of research papers concerning OM treatment published in 2007–2017 [22]. The authors described the substances used for prevention and treatment of OM, comprising, among others: a balm with *Lactobacillus Brevis* or royal jelly [22]. Other substances helpful in the treatment of OM were chamomile [23], calendula [11], aloe, curcumin [24], honey [14, 24, 25, 26], as well as vitamins C and E [13, 22, 26, 27].

**Chamomile** *(Matricaria recutita)* has the ability of inhibiting cyclooxygenase, 5-lipoxygenase and prostaglandins, and thus has anti-inflammatory and anti-microbic properties. It alleviates burning sensation and pain [9] and also has an anti-oxidating action, thus decreasing the amount of IL-1b and TNF-α [23].

**Aloe** *(Aloe vera)* has antipruritic, moisturising, anti-inflammatory and astringent properties. It is also a source of minerals, amino-acids, vitamins and fatty acids; moreover it is an immunostimulant with anti-cancer activity properties[9, 24].

**Vitamin E** has strong antioxidant action [26].

**Table I.** OM intensity scale according to WHO [10, 20, 21]

| OM intensity stage | Symptoms |
|---|---|
| 0 | no lesions |
| 1 | pain, erythema |
| 2 | erythema, erosions – yet the patient is able to eat solid food |
| 3 | ulceration – liquid diet is required |
| 4 | the patient is unable to consume fluids – parenteral nutrition |

**Honey** has an antibacterial and anti-inflammatory action [30], and, according to some experimental research, inhibits the initiation of NF-kB [14, 26].

Despite the extensive research which provides very positive evaluations of the above substances, available literature lacks any clear recommendations concerning their use in OM prevention and treatment in patients with head and neck cancers undergoing chemotherapy or radiotherapy. Prospective trials conducted on large groups of patients are necessary.

In 2014, the International Society of Oral Oncology (ISOO) and the Multinational Association of Supportive Care in Cancer (MASCC) published guidelines for treating patients with OM. The authors emphasise the role of oral hygiene in the prevention of the disease. They pay special attention to teeth brushing and rinsing the oral cavity [6, 8, 16].

In June 2019, the guidelines of MASCC/ISOO were updated and this revised version confirmed the previous guidelines concerning the basic rules of oral hygiene in OM prevention. The benefits from patients education were emphasised [28]. The study group MASCC/ISOO based this update on 9 source articles, 8 of which concern OM prophylaxis and treatment. The review concerned the principles of oral cavity care, the role of anti-inflammatory agents, natural substances, vitamins, dietary supplements, photo-biomodulation, and oral hygiene (tab. II). However, many binding guidelines have remained unchanged. The need for further research was stressed which might affect the next update of the guidelines [28–32].

What draws attention in the MASCC/ISOO guidelines from 2019 is an important change concerning the use of zinc and glutamine administered systemically [16, 31]. It is stressed that **zinc** is necessary for the correct functioning of the immune system and antibody production, as it has the ability to remove superoxide free radicals [9]. **Benzydamine**, in turn is a non-steroid anti-inflammatory drug – its efficacy has been proven in patients after irradiation treatment [22].

No recommendations concerning the administration of zinc, supersaturated *calcium phosphate rinse* (SCPR), an elemental diet and vitamin E [31] in the prevention of OM in patients with head and neck cancers undergoing RT and/or RT-CT were made. However, there was a suggestion of oral administration of glutamine in patients undergoing radiotherapy in order to prevent the development of OM. It must be remembered, however, that patients suffering from MS who are treated with hematopoietic stem cell transplantation (HSCT), should be administered glutamine with caution. In patients who received glutamine systemically, some treatment failures have occurred [31].

As a result of the lack of adequate number of trials, MASCC/ISOO did not publish any guidelines concerning the use of anti-inflammatory drugs, such as celexibe, misoprostol or rebamipide, for the prevention of OM in patients with head and neck cancers. In the OM prophylaxis, experts recommend rinsing the oral cavity with benzydamine in patients receiving

**Table II.** Interventions connected with radiotherapy in patients with head and neck cancer, published by MASCC/ISOO – guidelines update from 2019 [28–32]

| Intervention | Guideline |
|---|---|
| **Photo-biomodulation** – laser and other light therapies, intraoral low-power laser therapy | • OM prevention in patients with head and neck cancers:<br>– radiotherapy: change of the guidelines from suggestions to recommendations;<br>– patients in chemotherapy: novelty – use recommendation<br>• OM treatment: no guidelines |
| **Glutamine** – oral | • OM prevention in patients with head and neck cancer:<br>– radiotherapy: no guidelines<br>– radio-chemotherapy – use suggestion |
| **Elemental diet** | • no guidelines |
| **Zinc** | • OM prevention in patients with head and neck cancer:<br>– radio- or radio-chemotherapy: change – currently no guidelines |
| **Supplements**: vitamin E, selenium, folic acid, calcitriol | • no guidelines |
| **Rinsing** oral cavity with benzydamine | • OM prevention in patients with head and neck cancer:<br>– radiotherapy, dose up to 50 Gy: confirmation of the previous guidelines – rinsing oral cavity with benzydamine<br>– radio-chemotherapy: use suggestion<br>• OM treatment:<br>– radiotherapy: no guidelines<br>– radio-chemotherapy: no guidelines |

radiotherapy, as an independent treatment, up to a dose of 50 Gy [32]. It is also advisable to rinse the oral cavity with saline and calcium bicarbonate as this facilitates the maintenance of the correct oral hygiene for patients [28]. That said, similarly to the previous guidelines, chlorhexidine is not recommended as a mouth wash [28].

The MSCC/ISOO guidelines from 2014 concerning the prevention of oral mucositis in patients undergoing high-dose chemotherapy and whole body irradiation, before an autologous transplant of stem cells in the treatment of haematological cancers, recommend the use of palifermin [6, 8, 16]. **Palifermin** is a recombined human keratinocyte growth factor (KGF1), which affects the growth and differentiation of epithelial cells, playing also a role in inhibiting the process of apoptosis [5]. In spite of the promising results of the trials concerning the efficacy of this medication in OM prevention [22, 33, 34], there are also published reports about the adverse effects of this drug on cancers of the head and neck area treated with combined chemotherapy [35].

As a result of radiotherapy, reactive oxygen species (ROS) are produced which damage the cells of the mucous membrane. For the treatment of this condition, there were attempts to use the anti-oxidation enzyme: **superoxide dismutase** (SOD). A derivative of SOD, based on manganese, was produced and named **GC4419** – this substance has the ability to dissociate superoxide anions [5]. Barbor et al. described the beneficial the effect of this substance [36], including the results of the studies carried out by Anderson et al. are promising. In patients undergoing combined chemotherapy, after an intravenous administration of SOD, the intensification and duration of OM was decreased [37].

It must be remembered that it is prophylaxis that plays the key role in patients undergoing radiotherapy. That is why a patient qualified for irradiation of the head and neck area requires a thorough dental assessment and detailed instructions concerning oral hygiene. Correct oral care makes up a significant element of cancer patient treatment. Oral cavity hygenisation in order to remove potential inflammatory foci, requires the folowing procedures:

- completed treatment of cavities resulting from caries,
- correction of sharp filling edges,
- extraction of teeth not qualified for further treatment, and
- treatment of other inflammations within the oral cavity

It is necessary to control, and, if necessary, correct dentures and also to inform patients about nutritional requirements during radiotherapy. Sour, hot and overly hard products are not recommended. A large amount of fluid intake is recommended. The priority is to prevent any inflammatory condition within the oral mucosa as during anti-cancer treatment it is subject to irradiation. During oncological treatment the patient should be under the regular supervision of their dentist, so that a quick intervention in the case of inflammatory lesions within the oral cavity is possible [11].

Tables III and IV present detailed recommendations concerning prophylaxis and treatment in patients with symptoms of OM after radiotherapy, based on the selected, leading clinical recommendations [38].

For many years OM has been in the interest of dental associations. In 2015 the recommendation of the Polish Group of Specialists in Prophylaxis and Treatment of Complications within the Oral Cavity was published. The prophylactic and treatment procedures connected with irradiation were discussed in detail in this publication. These recommendations, in a brief from are presented in table V [39].

In 2009 Pytko-Polończyk proposed an algorithm of dental care in patients undergoing radio- and chemotherapy [40].

**Table III.** The comparison of the methods of oral mucositis (OM) prevention [38]

| |
|---|
| **Before the commencement of anti-cancer treatment**<br>• dental treatment<br>• prospective tooth extractions – 10–14 days before the planned radiotherapy |
| **During radiotherapy and after its completion (for ≥2 weeks)**<br>• washing teeth with a toothpaste and soft toothbrush (regularly exchanged ) ≥3 times per day<br>• using dental floss<br>• frequent drinking of small amounts of water and/or rinsing oral cavity with 0.9% saline, sodium bicarbonate or liquid containing benzydamine (Hascosept, Tantum verde) – 4–6 times per day<br>• not using the solutions of chlorhexidine and alcohol |
| **Absolutely forbidden**<br>• tobacco smoking<br>• alcohol consumption<br>• hot spices<br>• tough food |
| **It is recommended** to use ice cubes (only when there oral mucosa is not damaged) |

**Table IV.** The treatment of the patients with OM symptoms [38]

| Symptom | Recommendations |
|---|---|
| **Oral cavity dryness** | • sugar-free chewing gum, sugar-free sweets<br>• rinsing oral cavity with 0.9% NaCl solution or sodium bicarbonate<br>• artificial saliva |
| **Mild to moderate pain** | • local agents – benzocaine or benzydamine (used a few times per day onto the affected oral mucosa) |
| **Strong pain** | • analgesic treatment according to the WHO recommendations or rinsing with 0.2% morphine solution or 0.5% doxepin oral solution. |
| **Suspected infection** | • a swab followed by empirical treatment with a broad- spectrum antibiotic (aminoglycoside or 3$^{rd}$ generation cephalosporin) |
| **Suspected oral candidiasis** | • anti-fungal treatment |
| **Inability of oral consumption** | • parenteral nutrition to be considered |
| **Irrespectively of symptoms** | • zinc supplementation to be considered |

**Table V.** Recommendation of the Polish Group of Specialists in Prophylaxis and Treatment of Complications within the Oral Cavity [39]

| | |
|---|---|
| **Prophylaxis before treatment** | • oral hygiene (brushing teeth 3 times per day with a very soft toothbrush, rinsing oral cavity with 0.9% NaCl solution or with baking soda solution – 1 teaspoonful per 100 ml of boiled water, flossing)<br>• temporary removal of orthodontic appliance<br>• limitation of use of movable dentures<br>• dietary recommendations<br>• evaluation of the patient's nutrition status and, if necessary, gastrostomy tube feeding |
| **Preparation to head and neck irradiation** | • evaluation of the condition of oral cavity, orthopantomogram<br>• hygenisation of oral cavity<br>• conservative treatment, periodontology treatment with post-extraction wound dressing<br>• evaluation of prosthetic restorations<br>• removal of permanent dentures |
| **Patients in radiotherapy or chemotherapy – prophylaxis** | • proper oral hygiene<br>• brushing teeth with a soft toothbrush<br>• dental flosses<br>• cleaning of movable prosthetic restorations, at night – storing dentures in dry conditions<br>• oral cavity rinsing with 0.9% NaCl solution or baking soda solution – 5 times/day<br>• oral cavity rinsing with benzydamine 4 times/day<br>• oral cavity rinsing with – Caphosol solution 4–6 times/day<br>• oral cavity rinsing with – complex preparations – Alpha Med, laryngology mix<br>• secretion diluting agents<br>• fluoridation<br>• dietary consultation |
| **Patients in radiotherapy or chemotherapy – treatment** | • fungal infection – fluconazole 200–400 mg/day, nystatin – 5 times/day<br>• bacterial infection – antibiotic therapy according to the antibiogram or empirical<br>• Caphosol – rinsing oral cavity – 6–10 times/day<br>• benzydamine – 4 times/day |

| | |
|---|---|
| | • viral infection – acyclovir *p.o.*, *i.v.* to be considered<br>• analgesic treatment – medication and dose to be selected according to the WHO recommendations<br>• saliva substitutes<br>• high-protein and high-energy diet<br>• laser therapy |
| **Patients after healing of acute post-irradiation reaction** | • saliva substitutes<br>• dental consultation – evaluation of the oral cavity condition, hygiene instruction, soft toothbrushes, toothpaste with increased fluoride contents, brushing teeth after each meal, defects filling, fluoridation<br>• surgical intervention 6 months after the end of treatment with antibiotic cover<br>• dental check-up every 3 months |

Knowledge of the general principles of dental management in such patients should be, at least in general, known to oncology specialists, as this is an element of multispecialist patient care in cases of malignant cancers.

In **the first period**, before the commencement of anti-cancer treatments, a decontamination of the oral cavity should be performed. This process should be completed at least one week before the start of oncological treatment. This process comprises professional hygienisation procedures connected with detailed instructions for the patient, the removal of foci of inflammation and caries, filling the cavities and elimination of all traumatising factors. In **the second period**, during the anti-cancer treatment, a proper collaboration between the dentist and the oncology specialist is necessary. The procedures comprise the use of agents treating local lesions in the mucosa, including the first symptoms of OM and also the use of medication to alleviate xerostomia. The drugs which alleviate such lesions comprise a protein-free dialysate of calf blood (Solcoseryl paste; Meda), vitamin A + D3 in a fluid form, dental washes containing herbal mix, allantoin, D-panthenol, linseed (e.g. Alfa-med Atos, Alfa-implant Atos), a solution of calcium-phosphate ions (Caphosol [7, 40], Fomucal [41]). Also fluids containing benzydamine have a beneficial effect (Hascosept, Tantum verde) [38]. Often in patients after oncological treatment, it is necessary to introduce antibacterial and/or anti-mycotic treatments. It is recommended to have a low-carbohydrate diet, rich in vegetables and fruit, kephir and milk. The use of vitamin B is also helpful. The **third period** of dental care begins after the completion of oncological therapy, and is comprised of the continuation of the collaboration between the dentist and the patient, motivating them to maintain correct oral hygiene, the elimination of radiotherapy side-effects, such as: xerostomia, candidosis, bacterial infections. The patient should visit their dentist every one to three months and, then every three to six months [7, 40].

## Conclusions

Dentists play an important role in the prophylaxis of OM, especially in the multispecialist treatment of patients with cancers of the head and neck region who have developed symptoms of oral mucositis. That is why it is justifiable that oncological centres should create specialist teams, consisting of an oncologist, a dentist and a nurse. The members of these teams could provide multidisciplinary care to patients with head and neck cancers with regards to the prevention of OM and the treatment of this complication within the oral cavity.

**Conflict of interest:** none declared

**Katarzyna Szczeklik**
*Jagiellonian University Medical College*
*Institute of Dentistry*
*Department of Integrated Dentistry*
*ul. Montelupich 4*
*31-155 Kraków, Poland*
*e-mail: k.szczeklik@uj.edu.pl*

*Received: 12 May 2020*
*Accepted: 7 Sep 2020*

## References

1. http://onkologia.org.pl/nowotwory-zlosliwe-ogolem-2/.
2. Krajowy Rejestr Nowotworów. http://onkologia.org.pl/nowotwory-narzadow-glowy-i-szyi/.
3. Sonis ST. Pocket books for cancer supportive care. Oral mucositis. Springer Healthcare, Berlin 2012.
4. Shankar A, Roy S, Bhandari M, et al. Current trends in management of oral mucositis in cancer treatment. Asian Pacific Journal of Cancer Prevention. 2017; 18(8): 2019–2026, doi: 10.22034/APJCP.2017.18.8.2019.
5. Oronsky B, Goyal S, Kim M, et al. A Review of Clinical Radioprotection and Chemoprotection for Oral Mucositis. Translational Oncology. 2018; 11(3): 771–778, doi: 10.1016/j.tranon.2018.03.014.
6. Maria O, Eliopoulos N, Muanza T. Radiation-Induced Oral Mucositis. Frontiers in Oncology. 2017; 7, doi: 10.3389/fonc.2017.00089.
7. Zapała J, Wyszyńska-Pawelec G. Wybrane zagadnienia z onkologii głowy i szyi. Wydawnictwo Uniwersytetu Jagiellońskiego, Kraków 2017: 350–355.
8. Wysocki W, Małecki K. Zapalenia błony śluzowej związane z radioterapią i chemioterapią. Podsumowanie wytycznych MASCC/ISOO(2014r.). Medycyna praktyczna.pl. 2015. https://www.mp.pl/onkologia/wytyczne/111280.
9. Szałek E. Zapalenie błony śluzowej jamy ustnej – istotny problem terapeutyczny w onkologii. Farmacja Współczesna. 2018; 11: 8–14.
10. Dyszkiewicz M, Shaw H. Ocena stanu błony śluzowej jamy ustnej u pacjentów leczonych radio-i chemioterapią. Dent Med Probl. 2009; 46(1): 89–93.
11. Moslemi D, Nokhandani A, Otaghsaraei M, et al. Management of chemo/radiation-induced oral mucositis in patients with head and neck cancer: A review of the current literature. Radiother Oncol. 2016; 120(1): 13–20, doi: 10.1016/j.radonc.2016.04.001.
12. Sonis S. Mucositis: The impact, biology and therapeutic opportunities of oral mucositis. Oral Oncology. 2009; 45(12): 1015–1020, doi: 10.1016/j.oraloncology.2009.08.006.
13. Bockel S, Vallard A, Lévy A, et al. Pharmacological modulation of radiation-induced oral mucosal complications. Cancer/Radiothérapie. 2018; 22(5): 429–437, doi: 10.1016/j.canrad.2017.11.006.
14. Debraj HD, Singh V, Mohammad S, et al. Effect of Topical application of pure honey in chemo-radiation-induced mucositis and its clinical benefits in improving quality of life in patients of oral squamous cell carcinoma . International Journal of nursing studies. 2019; 89(2019): 80–87.

15. Sroussi H, Epstein J, Bensadoun RJ, et al. Common oral complications of head and neck cancer radiation therapy: mucositis, infections, saliva change, fibrosis, sensory dysfunctions, dental caries, periodontal disease, and osteoradionecrosis. Cancer Med. 2017; 6(12): 2918–2931, doi: 10.1002/cam4.1221.
16. Lalla R, Bowen J, Barasch A, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer. 2014; 120(10): 1453–1461, doi: 10.1002/cncr.28592.
17. Mierzwa D, Hadzik J, et al. Pyrek Profilaktyka i leczenie zmian w jamie ustnej wywołanych chemioterapia i radioterapia onkologiczną przegląd piśmiennictwa. Bestom Dentonet.pl. 2014; Edentico 2(48): 14.8–14.13.
18. Woźniak M, Czyż M. Mimetyki dysmutazy ponadtlenkowej- potencjalne zastosowania kliniczne. Postępy Hig Med. 2008; 62: 613–662.
19. OncoLink Team.Mucositis (Mouth Sores) &Oral Care Tip Sheet 2018. www.oncolink.org.
20. WHO handbook for reporting results of cancer treatment. World Health Organization 1979. http://www.who.int/iris/handle/10665/37200.
21. Kornaś-Burek A, Lipska W, Darczuk D, et al. Mucositis-współczesne poglądy na rozpoznanie i leczenie Journal of stomatology. Journal of stomatology. 2014; 67(1): 114–127.
22. Daugėlaitė G, Užkuraitytė K, Jagelavičienė E, et al. [Exercise therapy in myocardial infarction according to the Republican Clinical Hospital in Kaunas]. Sveikatos Apsauga. 1962; 7(3)(5): 54–781, indexed in Pubmed: 13883679.
23. Gomes V, Gomes RN, Gomes M, et al. Effects of Matricaria Recutita (L.) in the Treatment of Oral Mucositis. The Scientific World Journal. 2018; 2018: 1–8, doi: 10.1155/2018/4392184.
24. Yu YY, Deng JL, Jin XR, et al. Effects of 9 oral care solutions on the prevention of oral mucositis: a network meta-analysis of randomized controlled trials. Medicine (Baltimore). 2020; 99(16): e19661, doi: 10.1097/MD.0000000000019661, indexed in Pubmed: 32311938.
25. Münstedt K, Momm F, Hübner J. Honey in the management of side effects of radiotherapy- or radio/chemotherapy-induced oral mucositis. A systematic review. Complement Ther Clin Pract. 2019; 34: 145–152, doi: 10.1016/j.ctcp.2018.11.016, indexed in Pubmed: 30712719.
26. Thomsen M, Vitetta L. Adjunctive Treatments for the Prevention of Chemotherapy- and Radiotherapy-Induced Mucositis. Integr Cancer Ther. 2018; 17(4): 1027–1047, doi: 10.1177/1534735418794885, indexed in Pubmed: 30136590.
27. Yang C, Gong G, Jin E, et al. Topical application of honey in the management of chemo/radiotherapy-induced oral mucositis: A systematic review and network meta-analysis. Int J Nurs Stud. 2019; 89: 80–87, doi: 10.1016/j.ijnurstu.2018.08.007.
28. Hong C, Gueiros L, Fulton J, et al. Systematic review of basic oral care for the management of oral mucositis in cancer patients and clinical practice guidelines. Supportive Care in Cancer. 2019; 27(10): 3949–3967, doi: 10.1007/s00520-019-04848-4.
29. Elad S. The MASCC/ISOO Mucositis Guidelines 2019 Update: introduction to the first set of articles. Support Care Cancer. 2019; 27(10): 3929–3931, doi: 10.1007/s00520-019-04895-x, indexed in Pubmed: 31286226.
30. Zadik Y, Arany PR, Fregnani ER, et al. Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO). Systematic review of photobiomodulation for the management of oral mucositis in cancer patients and clinical practice guidelines. Support Care Cancer. 2019; 27(10): 3969–3983, doi: 10.1007/s00520-019-04890-2, indexed in Pubmed: 31286228.
31. Yarom N, Hovan A, Bossi P, et al. Mucositis Study Group of the Multinational Association of Supportive Care in Cancer / International Society of Oral Oncology (MASCC/ISOO). Systematic review of natural and miscellaneous agents for the management of oral mucositis in cancer patients and clinical practice guidelines-part 1: vitamins, minerals, and nutritional supplements. Support Care Cancer. 2019; 27(10): 3997–4010, doi: 10.1007/s00520-019-04887-x, indexed in Pubmed: 31286229.
32. Ariyawardana A, Cheng K, Kandwal A, et al. Systematic review of anti-inflammatory agents for the management of oral mucositis in cancer patients and clinical practice guidelines. Supportive Care in Cancer. 2019; 27(10): 3985–3995, doi: 10.1007/s00520-019-04888-w.
33. Le QT, Kim H, Schneider C, et al. Palifermin Reduces Severe Mucositis in Definitive Chemoradiotherapy of Locally Advanced Head and Neck Cancer: A Randomized, Placebo-Controlled Study. J Clin Oncol. 2011; 29(20): 2808–2814, doi: 10.1200/jco.2010.32.4095.
34. Henke M, Alfonsi M, Foa P, et al. Palifermin Decreases Severe Oral Mucositis of Patients Undergoing Postoperative Radiochemotherapy for Head and Neck Cancer: A Randomized, Placebo-Controlled Trial. J Clin Oncol. 2011; 29(20): 2815–2820, doi: 10.1200/jco.2010.32.4103.
35. Bockel S, Vallard A, Lévy A, et al. Pharmacological modulation of radiation-induced oral mucosal complications. Cancer/Radiothérapie. 2018; 22(5): 429–437, doi: 10.1016/j.canrad.2017.11.006.
36. Barbor M. Novel therapy reduces duration of chemoradiotherapy-inducedmucositis in patients with head and neck cancer. The Asco Post, 2018 .
37. Anderson C, Lee C, Saunders D, et al. Phase IIb, Randomized, Double-Blind Trial of GC4419 Versus Placebo to Reduce Severe Oral Mucositis Due to Concurrent Radiotherapy and Cisplatin For Head and Neck Cancer. J Clin Oncol. 2019; 37(34): 3256–3265, doi: 10.1200/jco.19.01507.
38. Hetnał M, Wysocki W. Popromienne zapalenie błony śluzowej jamy ustnej. Interna Szczeklika 2019. Medycyna Praktyczna, Kraków 2019.
39. http://szpiczak.org/wp-content/uploads/aktualnosci/artykuly/2015/rekomendacje_dla_lekarzy_i_piel%C4%99gniarek_2015_poprawiony.pdf.
40. Pytko-Polończyk J. Analiza stanu klinicznego i zmian mikroflory jamy ustnej w przebiegu radioterapii chorych na raka narządów głowy i szyi jako podstawa opracowania algorytmu stomatologicznego leczenia wspomagającego. Wydawnictwo Uniwersytetu Jagiellońskiego, Kraków 2009.
41. http://www.90c.pl/3r/files/4115/4349/5555/Powiklania_popromienne_w_jamie_ustnej.pdf.