http://dx.doi.org/10.35630/2199-885X/2020/10/4.30

MICROCIRCULATORY ALTERATIONS IN PATIENTS WITH OROPHARYNGEAL CANCER AFTER RADIATION THERAPY: A POSSIBLE CORRELATION WITH MUCOSITIS?

Received 23 September 2020;
Received in revised form 15 October 2020;
Accepted 20 October 2020

***Hoang Giao Nguyen*[1,2]✉, *Anatoly Avanesov*[1,2], *Evgenia Gvozdikova*[1,2], *Elena Kandakova*[1], *Liudmila Kruchinina*[2], *Yuri Alimov*[3], *Dalila Ali Khaydar*[1,2], *Sergey Golub*[1,2]**

[1] *National Medical Research Radiological Center, Moscow, Russia*
[2] *Peoples' Friendship University of Russia, Moscow, Russia*
[3] *N.N. Blokhin National Medical Research Center of Oncology, Moscow, Russia*

✉ *drgiaohoang2505@gmail.com*

ABSTRACT — Background: Patients affected by several forms of malignant neoplasms receive chemotherapy (CT) or radiation therapy (RT). These treatments can cause many side effects, such as oral mucositis (OM).
Mucositis is the most frequently occurring early side effect of conservative treatment of patients with malignant tumors in the head and neck, and it is registered in more than 60% of cases. It occurs due to the effect of chemotherapeutic drugs on the cells of the mucous membrane, which causes their death, and to a greater extent, due to the effect of ionizing radiation on the endothelium of the blood vessels and the basal cells of the mucous membrane the submucosa. Objectives: To assess the correlation between the indicators of hemomicrocirculation of the oral mucosa and the intensity of the clinical manifestations of oral mucositis. Materials and Methods: This study included 48 patients who had a morphologically confirmed diagnosis of squamous cell carcinoma and received radiation therapy at National Medical Research Radiological Centre (Moscow, Russia). Results: It was found that, in all the subgroups, the severity index of mucositis National Cancer Institute (NCI) clearly correlated with the indicators of the flow of microcirculation through the study area at point A (r = -0.85, -0.99 and -0.77). At point A, blood perfusion in the study of hemomicrocirculation in all the subgroups 18–44 g in Ia, 45–59 g and 60–74 g in Ic was the opposite of the value of the severity of mucositis. A strong negative correlation was found between the severity of mucositis and the perfusion index at point B in subgroup Ia : (r = -0.99) along with, a moderate inverse correlation in subgroups Ib (r = -0.69) and Ic (r = -0.36). At point B, a strong inverse correlation was found in subgroups Ib and Ic (r = -0.72 and -0.65, respectively), and a moderate inverse correlation was found in subgroup Ia — NCI where r = -0.32. Conclusions: There is a negative correlation between the indicators of hemomicrocirculation of the oral mucosa and the severity of oral mucositis. It was found that the higher the lesions of the microvasculature, the lower the intensity of mucositis. These data have important prognostic value and make it possible to recommend the determination of hemomicrocirculation as a screening test.

KEYWORDS — mucositis, oral cavity, radiation therapy, microcirculation, correlation.

BACKGROUND

Patients affected by several forms of malignant neoplasms receive chemotherapy (CT) or radiation therapy (RT). These treatments can cause many side effects, such as oral mucositis (OM).

Mucositis is the most frequent early side effect of conservative treatment of patients with malignant tumors in the head and neck, and it is registered in more than 60% of cases. It occurs due to the effect of chemotherapeutic drugs on the cells of the mucous membrane, which causes their death, and to a greater extent, due to the effect of the ionizing radiation on the endothelium of the blood vessels and basal cells of the mucous membrane, the submucosa.

The pathogenesis of OM provides for a vascular phase at the onset of lesions in the oral cavity, but the literature lacks data on the correlation between OM and the changes in microcirculation in the oral cavity. Avanesov A.M. described the dependence of the hemomicrocirculation indices in the oral mucosa in patients diagnosed with squamous cell carcinoma of the oropharyngeal region on the severity of clinical manifestations of mucositis (2018) (5). Other researchers have assessed the perfusion of the oral mucosa by monitoring and quantifying the density of the capillaries before and after the administration of CT and RT in cancer patients (Gvozdikova E.N. 2017) (8). This study shows that there is a relationship between the state of hemomicrocirculation of the oral mucosa and the intensity of oral mucositis.

Objective:

to assess the correlation between the indicators of hemomicrocirculation of the oral mucosa and the intensity of the clinical manifestations of oral mucositis.

MATERIALS AND METHODS

This study included 48 patients who had a morphologically confirmed diagnosis of squamous cell carcinoma and received radiation therapy. All the patients underwent treatment at the Department of Radiotherapy, National Medical Research Radiological Centre (NMRRC), Russian Federation. All the patients were divided into 3 age groups:

Ia — patients from 18 to 44 years of age
Ib — patients from 45 to 59 years of age
Ic — patients from 60 to 74 years of age.

The average age of the patients was 53 years. The patients comprised 32 men and 16 women. Ib was the largest group, and 28%.

Localization of malignant neoplasms was dominated by lesions of the tongue (13%), the bottom of the oral cavity (8.3%), the upper jaw (7%), the oropharynx (45.8%), the nasopharynx (7%), and the tumors of other localizations (lesions of the lip, cheek, and alveolar ridge of the lower jaw) accounted for 18.9%.

The division into subgroups was based on the voluntary consent of the patients to follow the recommendations of the dentist and to use the prescribed treatment regimens for the prevention and treatment of mucositis in the presence of radiation. All the patients of the subgroups Ia, Ib, and Ic received daily local dental treatment according to the following guidelines:

1. During irradiation, patients should avoid consuming hot, spicy, solid food and alcohol and should stop smoking.

2. They should brush their teeth using a soft-bristled brush 2 times a day (morning and evening). Patients are advised to use a paste without irritating substances, such as toothpastes manufactured for babies. The use of dental floss (dental floss) is prohibited.

3. They should rinse their mouth with broths of sage, chamomile, and long-acting drug Tonsinal 6–8 times a day. After eating, they should rinse their mouth with antiseptic solutions of Chlorhexidine (0.05%) or Miramistin (0.01%). After rinsing, it is recommended to apply castor oil to the mucous membrane of the mouth for moisturization. The use of alcohol containing rinses for the prevention and treatment of mucositis is contraindicated.

4. They should moisturize their lips with petroleum jelly and hygienic lipstick 3–4 times a day.

5. The use of removable dentures is not recommended since it can lead to excessive irritation of the mucous membrane and increase the pain syndrome. The use of partial or complete dentures should be minimized or avoided.

6. They should ensure daily applications of CM-1 plates and Pharmadont 1–2 plates (which were prescribed depending on the severity of clinical symptoms) 2–3 times a day.

7. The control of the level of individual hygiene and measurement of hemomicrocirculation for each stage of radiation therapy should be as follows: before irradiation, 0–20 Gy, 22–40 Gy, 42Gy, and more, and after irradiation, at the dentist.

To determine the parameters of microcirculation, 48 patients of the 1st group were checked before and after undergoing radiation therapy and administered with doses at the rate of 0–20 Gy, 22–40 Gy, 42 Gy and more during its various stages. Measurements were taken at four randomly selected points: A — mucous membrane of the alveolar gums in the area of teeth 11 and 21; B — the mucous membrane of the lower lip in the projection of the site of the infestation; C — the mucous membrane of the cheek in the projection of teeth 16 and 17; D — the mucous membrane at the bottom of the oral cavity in the projected area where the tongue was attached with the help of the Apparatus Lacc M device (2nd version) (refer to Fig. 1) in the dental office of the NMRRC.

Fig. 1. *Apparatus Lacc M (2nd version)*

The apparatus Lacc-M light guide analyzer ensures the delivery of probe radiation from the laser to the research area and its transport to the photodetectors of radiation reflected from the tissue containing silica in serum.

While interacting with tissue, the reflected signal contains a component produced by the reflection from the moving red blood cells, which is proportional to the speed of movement (Doppler effect). The amplitude of the signals in the device is formed by

all erythrocytes located in the probing region, which move at different speeds and with different numbers and are distributed in the arterioles, capillaries, venules, and arteriovenular anastomoses. At the output of the LACC 02, a signal is formed, which is an indicator of microcirculation PM):

$$PM = Ner \times Vcr$$

where Ner is the number of erythrocytes in the probe volume, Vcr is the average rate of erythrocytes.

The state of microcirculation was assessed according to several parameters with the help of Laser Doppler flowmetry (LDF)

M — the average value of the microcirculation indicator, i.e., the average blood flow in a given time interval in perfusion units, which characterizes the tissue hemomicroperfy;

σ — the root mean square deviation of the amplitude of the oscillation of the blood flow, and it reflects, among other things, the elasticity of the wall of the blood vessel

Kv — the coefficient of variation, i.e., the ratio of σ to M, and it is the most objective parameter that allows the assessment of the state of microcirculation as a whole.

Given the small number of observations, the statistical processing was carried out by using the sign test (a non-parametric method).

Ethical approval for our study was obtained (No. 0318) from the Ethics Committee of the Institute of Medicine, Peoples' Friendship University of Russia, Moscow, Russia.

RESULTS AND DISCUSSION

The results are presented in Tables 1, 2, 3, and 4.

It was found that, in all the subgroups, the severity index of mucositis NCI clearly correlated with the indicators of the flow of microcirculation through the study area at point A: NCI — subgroup Ia (r = -0.85); NCI — subgroup Ib (r = -0.99) NCI — subgroup Ic (r = - 0.77). The (Pearson) correlation coefficient was close to -1, which means that there was a strong negative correlation between the variables. In other words, at point A, blood perfusion in the study of hemomicrocirculation in all the subgroups 18–44 in Ia, 45–59 in Ib and 60–74 in Ic was opposite to the value of the severity of mucositis. It was found that the severity of mucositis will decrease with the increase in blood perfusion in the study of microcirculation.

The results of the ratio of the severity of mucositis to the hemomicrocirculation index at point B are presented in Table 2.

A strong negative correlation was found between the severity of mucositis and the perfusion index at point B in subgroup Ia (r = -0.99), and a moderate inverse correlation was found in subgroups Ib (r = -0.69) and Ic (r = -0.36).

Table 3 shows that at point C, a strong inverse correlation was found between the severity of mucositis and the hemomicrocirculation indices in the subgroups Ib and Ic (Ib — NCI: r = -0.72, Ic — NCI: r = -0.65) and a moderate inverse correlation was found in subgroup Ia (Ia — NCI: r = - 0.32). This indicates that at point B, the increase in the severity of mucositis, which we found in the patients in subgroup Ia, was higher than that in the rest even though the microcirculation indices in all the subgroups tended to recover. The frequency and severity of oral mucositis in subgroup Ia changed more slowly. This suggests that other factors also affected the microcirculation indices in the buccal mucosa in the projection of teeth 16 and 17 in subgroup Ia.

As can be observed in Table 4, the correlation coefficient for all the subgroups has negative values. However, in group Ia, the intermediate values were close to 0 (r = -0.04), which indicates a weak correlation between the severity of mucositis and the indicators of hemomicrocirculation in the mucous membrane of the floor of the mouth in the projection of the frenulum attachment site language. However, in subgroup Ib — NCI: r = -0.5 and Ic — NCI: r = -0.73, there was a strong negative correlation. This indicates a strong relationship between the indicators of hemomicrocirculation of the blood vessels and the intensity of clinical manifestations of oral mucositis.

CONCLUSION

The comparative analysis of the effectiveness of local treatment, depending on the age of the patients, demonstrated a higher efficiency of dental support in the age groups of 18–44 years and 45–59 years and a lower efficiency in the age group of 60–74 years.

It was found that radiation therapy causes changes in the hemomicrocirculation of the tissues of the oral mucosa. The tissue perfusion rates were reduced by up to 50% depending on the age group. After dental support, there was a 12.4% decrease in subgroup Ia, a 24.5% decrease in group Ib and a 33.4% decrease in subgroup Ic.

There is a negative correlation between the indicators of hemomicrocirculation of the oral mucosa and the severity of oral mucositis. The higher the lesions of the microvasculature, the lower is the intensity of mucositis. These data have important prognostic value and make it possible to recommend the determination of hemomicrocirculation as a screening test.

Table 1. *Hemomicrocirculation at point A versus NCI severity of oral mucositis*

Measurement point	Subgroups	Before radiation therapy	0–20 Gy	22–40 Gy	42 Gy and more	After treatment	Correlation coefficient (r)
Point A	Ia (18–44 years)	44.70	32.28	34.19	31.08	34.03	-0.85
	NCI	0	0.89	0.67	1.11	0.22	
	Ib (45–59 years)	35.78	23.94	25.13	23.66	26.23	-0.99
	NCI	0	0.29	0.21	0.36	0.07	
	Ic (60–74 years)	24.55	13.94	16.29	12.95	15.61	-0.77
	NCI	0	0.73	0.55	0.91	0.18	

Table 2. *Hemomicrocirculation at point B versus NCI severity of oral mucositis*

Measurement point	Subgroups	Before radiation therapy	0–20 Gy	22–40 Gy	42 Gy and more	After treatment	Correlation coefficient (r)
Point B	Ia (18–44 years)	19.51	14.82	15.72	13.87	16.73	-0.99
	NCI	0	0.89	0.67	1.11	0.22	
	Ib (45–59 years)	20.48	10.48	16.14	11.77	14.95	-0.70
	NCI	0	0.29	0.21	0.36	0.07	
	Ic (60–74 years)	18.11	5.45	9.08	6.33	7.02	-0.36
	NCI	0	0.73	0.55	0.91	0.18	

Table 3. *Hemomicrocirculation at point C versus NCI severity of oral mucositis*

Measurement point	Subgroups	Before radiation therapy	0–20 Gy	22–40 Gy	42 Gy and more	After treatment	Correlation coefficient (r)
Point C	Ia (18–44 years)	20.07	14.02	15.97	14.16	17.29	-0.32
	NCI	0	1.78	1.33	1.44	1.56	
	Ib (45–59 years)	18.32	9.49	16.39	10.74	13.82	-0.72
	NCI	0	0.57	0.43	0.46	0.5	
	Ic (60–74 years)	18.11	10.53	17.42	10.18	13.09	-0.65
	NCI	0	1.45	1.09	1.18	1.27	

Table 4. *G-point hemomicrocirculation index versus NCI severity of oral mucositis*

Measurement point	Subgroups	Before radiation therapy	0–20 Gy	22–40 Gy	42 Gy and more	After treatment	Correlation coefficient (r)
Point D	Ia (18–44 years)	16.50	12.42	13.88	11.80	14.44	-0.04
	NCI	0	1.56	1.11	1.44	1.67	
	Ib (45–59 years)	14.87	5.91	12.39	8.26	10.76	-0.50
	NCI	0	0.5	0.36	0.46	0.54	
	Ic (60–74 years)	11.63	5.95	9.52	7.00	7.74	-0.73
	NCI	0	1.27	0.91	1.18	1.36	

DISCUSSION OF THE RESULTS

There is no gold standard for cancer treatment. Cancer treatment usually includes surgery, RT, CT, or a combination of these on an individual basis. The administration of these agents can determine the onset of oral lesions such as oral stomatomucositis (4). The risk factors leading to the development of oral post-radiation mucositis are versatile: chronic alcohol consumption, cigarette smoking, low body mass index (BMI < 18.5) as well as concomitant diseases, such as diabetes mellitus, hypertension, and atherosclerosis.

This study showed that the PM microcirculation index in patients varies unevenly throughout the entire stage of radiation and/or chemotherapy. An increase in microcirculation indices reached the maximum point at a dose of 20–28 Gy, which corresponded, on average, to the first clinical manifestations of oral mucositis in the patients (hyperemia and swelling of the mucous membrane), followed by a decrease in the indicator to values that were 49.6% less than the initial values.

In our study, we noted that there is a negative correlation between the indicators of hemomicrocirculation of the oral mucosa and the severity of oral mucositis. The higher the lesions of the microvasculature, the lower is the intensity of mucositis. These data have important prognostic value and make it possible to recommend the determination of hemomicrocirculation as a screening test.

REFERENCES

1. **Avanesov A., Gvozdikova E., Hoang N.G., Darawsheh H., Kandakova E., Alimov Y., Anastasia Ignatova, Abusinova Z., Muravyeva A.** Hemomicrocirculation of the oral mucosa as an efficiency indicator of local treatment and preventing complications from radiation and chemotherapy for head and neck malignancies. Archiv Euromedica, 2020; 10 (1), 146–150. 10.35630/2199-885X/2020/10/41
2. **Avanesov A.M., Gvozdikova E.N.** Prognostic factors determining the clinical course of oral mucositis in patients with squamous cell carcinoma of the oropharyngeal region – RUDN Bulletin. Series: MEDICINE, 2018; 22 (1): 22–28.
3. **Ferlay J., Soerjomataram I., Ervik M., Dikshit R., Eser S., Mathers C., et al.** GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11
4. **Field L.P.** Radiation stomatitis. SPb. Nordmedizdat. 2014. 132.
5. GBD 2015 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016 Oct; 388 (10053): 1659–1724.
6. **Gianni L., Baselga J., Eiermann W., Porta V.G., Semiglazov V., Lluch A., Zambetti M., Sabadell D., Raab G., Cussac A.L., Bozhok A., MartinezAgullo A., Greco M., Byakhov M., Lopez J.J., Mansutti M., Valagussa P., Bonadonna G.** 2009. Phase III trial evaluating the addition of paclitaxel to doxorubicin followed by cyclophosphamide, methotrexate, and fluorouracil, as adjuvant or primary systemic therapy: European Cooperative Trial in Operable Breast Cancer. J Clin Oncol; 27: 2474–2481.
7. **Haagen J., Krohn H., Rollig S., Schmidt M., Wolfram K., Dorr W.** 2009. Effect of selective inhibitors of inflammation on oral mucositis: Preclinical studies. Radiother Oncol 92: 472–476.
8. **Khaw A., Logan R., Keefe D., Bartold M.** Radiation-induced oral mucositis and periodontitis - proposal for an inter-relationship. Oral Diseases. 2014; 20 (3): 7–18. DOI: 10.1111 / odi.12199
9. **Kotlova O.V.** The functional state of periodontal tissues and microbiocenosis of the oral cavity in young people of the Arkhangelsk region: Ph.D. thesis. Arkhangelsk. 2001. 83.
10. **Krasnoperova L. D.** Raltitrexide in the chemoradiation treatment of malignant neoplasms of the head and neck: Ph.D. thesis. Ufa 2007. 101.
11. **Lall R.V., Latortue M.C., Hong C.H., et al.** A systematic review of oral fungal infections in patients receiving cancer therapy. Support Care Cancer. 2010; 18 (8): 985–992.
12. **Lalla R.V., Peterson D.E.** Oral mucositis. Dent Clin North Am. 2005. 49 (1): 167–184.
13. **Levendag P.C., Nijdam W.M., van Moolenburgh S.E., et al.** Interstitial radiation therapy for early-stage nasal vestibule cancer: a continuing quest for optimal tumor control and cosmesis. Int J Radiat Oncol Biol Phys. 2006; 6 (1): 160–169.
14. **Lyon, France:** International Agency for Research on Cancer; 2013.
15. **Murphy B.A., Beaumont J.L., Isitt J., Garden A.S., Gwede C.K., Trotti A.M., Meredith R.F., Epstein J.B., Le Q.T., Brizel D.M., Bellm L.A., Wells N., Cella D.** 2009. Mucositis-Related morbidity and resource utilization in head and neck cancer patients receiving radiation therapy with or without chemotherapy. J Pain Symptom Manage; 38: 522–532.
16. **Otmani N.** Oral and maxillofacial side effects of radiation therapy on children. J Can Dent Assoc 2007; 73 (3): 257–61.
17. **Plummer M., de Martel C., Vignat J., Ferlay J., Bray F., Franceschi S.** Global burden of cancers attributable to infections in 2012: a synthetic analysis. Lancet Glob Health. 2016 Sep;4 (9): e609–16. DOI: 10.1016/S2214-109X(16)30143-7.
18. **Rosenthal D.I., Trotti A.** Strategies for managing radiation-induced mucositis in head and neck cancer. Semin Radiat Oncol 2009; 19 (1): 29–34.

19. **S Saito N, Imai Y., Muto T., Sairenchi T.** Low body mass index as a risk factor of moderate to severe oral mucositis in oral cancer patients with radiotherapy. Support Care Cancer. 2012 Dec 1; 20 (12): 3373–3377. DOI: 10.1007/s00520–012–1620–7
20. **Sonis S., Haddad R., Posner M., et al.** Gene expression changes in peripheral blood cells provide insight into the biological mechanisms associated with regimen-related toxicities in patients being treated for head and neck cancers. Oral Oncol. 2007; 43 (3): 289–300.
21. **Sonis S.T.** Oral mucositis in cancer therapy. J Support Oncol. 2004; 2 (): 3–8.
22. **Sonis S.T.** Oral mucositis. Anticancer Drugs. 2011. 22 (7): 606–612.
23. **Sonis ST.** 2007. Pathobiology of oral mucositis: Novel insights and opportunities. J Support Oncol; 5 (9 Suppl 4): 3–11.
24. **Stewart B.W., Wild C.P.**, editors. World cancer report 2014. Lyon: International Agency for Research on Cancer; 2014
25. **Tao Z., Gao J., Qian L., Huang Y., Zhou Y., Yang L., et al.** Factors associated with acute oral mucosal reaction induced by radiotherapy in head and neck squamous cell carcinoma: A retrospective single-center experience. Medicine 2017 Dec; 96 (50): e8446. DOI: 10.1097/MD.0000000000008446
26. The status of cancer care for the population of Russia in 2015. Ed. HELL. Kaprina V.V., Starinsky G.V., Petrova M. 2016. 236 p.
27. **Vorobyov Y.I., Garbuzov M.M., Retinskaya I.I.** Clinic, diagnosis and principles of radiation treatment of malignant neoplasms of the mucous membrane of the cheek Dentistry, 2000; No 1. S. 36–38 p.
28. **Xu L., Zhang J., Lui J., et al.** Investigation of the oral infections and manifestations seen in patients with advanced cancer. J Med Sci. 2013; 29 (5): 1112–1115.