JMS 2022;5(1):172-178
UDC: 616.316-008.64:617.51/.53-006.6-085.849
DOI:10.55302/JMS2251172rgj

IMPACT OF INTENSITY MODULATED RADIATION THERAPY ON THE SALIVARY GLANDS FUNCTION AND SALIVA FLOW RATE

Sonja Rogoleva Gjurovski[1], Vladimir Popovski[2], Lenche Kostadinova[3], Bruno Nikolovski[1]
[1]Faculty of Medical Sciences, University Goce Delcev, Stip, R. North Macedonia
[2]University Clinic for Maxillofacial surgery, Faculty of Dentistry, Ss. Cyril and Methodius, University in Skopje, R. North Macedonia
[3] University Clinic of Radiotherapy and Oncology, Skopje, R. North Macedonia

Abstract

In patients with head and neck cancer, the most common issue after radiation treatment is xerostomia and the consequences of that, which are affecting the quality of everyday life of the patient. Subjectively xerostomia is manifested as dryness in the oral cavity, followed with obstructed chewing and swallowing of the food.

Mostly it happens because of the death of the cells in the gland that are supposed to be dividing, caused by the radiation. To improve patients' life after treatment, IMRT approach has been considered to be a better solution for the gland tissue sparing during the radiation treatment, therefore, to decrease the severity and the intensity of the following xerostomia.

The IMRT technique allows the chosen dose of radiation to be applied specifically on the tissue where it is supposed to be, sparing the surrounding healthy parts from the unnecessary radiation.

The aim of this study was to evaluate the influence of the Intensity Modulated Radiation therapy (IMRT), with different intensity and dosage, on the function of salivary glands.

For this study were analyzed total number of 87 surveys, 41 of them were used for detail analysis. This study is based on narrative review on published articles written in English language, reporting results related to the use of Intensity modulated radiation therapy treatment in patients with head and neck cancer.

The gathered results have shown that the function of the salivary glands after radiation treatment can be in many cases protected during the treatment, or even restored to some level, therefore the resulting xerostomia can be reduced and its' following negative effects affecting the patients' life could be minimized by using the improved technique IMRT.

In many studies the evaluated levels of xerostomia have been found to be significantly lower in the groups of patients treated with IMRT technique, compared with the other group of patients treated with conventional radiation therapy. Also, a big influence has the dosage of the radiation beams, on what depends on the outcome of the salivation function in patients treated with radiation therapy.

Keywords: Intensity modulated radiation therapy, xerostomia, salivary glands hypo-function, saliva reduction, saliva flow rate, salivary gland sparing.

Introduction

As a consequence of radiation therapy, xerostomia and dysphagia are the most common occurrences in patients with head and neck cancer, therefore these two most common issues are the main factors that cause disruption to the normal speech and swallowing, that also affects the quality of everyday life in these patients [1].

The xerostomia subjectively it is manifested as uncomfortable feeling of dryness in the mouth, the oral mucosa, caused by reduced saliva production and flow in a minute, that most often is under 0.1 to 0.2 mL in a minute [2,3].

Radiation induced DNA damage of the glandular cells obstructs the proper cell division what results in cell death or senescence of cells that are supposed to divide. Radiation caused injury in the glands induces loss of the specific saliva-producing acinar cells, however the ducts of glands although are deprived of function but they in most of the cases remain intact. Study has found that if the dose range is low (< 30 Gy, in 2 Gy fractions) the damage that is following is reversible to a certain part, but

if the doses are cumulative (> 75 Gy) the consequences are extensive degeneration of acini followed with inflammation and fibrosis in the interstitium of the salivary glands [3].

However, the xerostomia is not always related to saliva flow reduction, so it can also be manifested independently [4]. When xerostomia is manifesting as a consequence of radiation therapy, in most of the cases it is irreversible and permanent [4,5].

The treatment volumes with radiation therapy are often huge in order to cover all the parts with the disease and the risky cervical nodes, therefore bilateral neck irradiation is often demanded [6,7].

In the latest surveys it has been shown that with implementation of the new technique, modified radiotherapy (IMRT – Intensity Modulated Radiation Therapy), the incidence of xerostomia has been reduced in a big part [7,8].

Intensity modulated radiation therapy (IMRT) planning makes it possible for high doses to be applied in the targeted area. The consequences after treatment has been proven that is connected to the dose of radiation that is applied on the salivary glands during the radiotherapy treatment [8,9].

The submandibular glands have been much less investigated, but their function is also very important. The submandibular glands are responsible for about 90% of the unstimulated saliva, it is assumethat with lowering the dose of radiation in the submandibular gland, it can also improve the biggest part of the salivary function [10,11].

Intensity-modulated radiation therapy (IMRT) is an advanced and improved type of radiotherapy that is highly precise method, it is based on using computer-controlled linear accelerators to apply precise radiation doses to the specific places where the tumor tissues are affected [12,13].

IMRT technique makes it possible for the radiation dose to be more precisely applied in three-dimensional (3-D) shape of the treated tumor, by modulating the intensity of the radiation beams in multiple small parts [13,14]. This method of radiation therapy also helps the higher doses of radiation to be focused specifically on the tumor, while minimizing the exposure on radiation to surrounding normal healthy structures. The treatments are carefully planned with using 3-D computed tomography (CT) or magnetic resonance (MRI) images of the patients, that are combined with calculated dose of radiation, to determine the exact dose intensity pattern that will give the best result for each case individually [15,16].

The aim of this study was to evaluate the influence of the Intensity Modulated Radiation therapy (IMRT), with different intensity and dosage, on the function of salivary glands in patients with head and neck cancer, treated with radiation therapy.

Material and methods

Research strategy

For this study were analyzed total number of 87 surveys. This survey was based on narrative reviews from published studies, that have investigated the topic the use of Intensity modulated radiation therapy treatment in patients with head and neck cancer.

The research was done using the data bases of PubMed (Medline), NCBI (US National Library of Medicine), Medscape, Webmd, Mdconsult, Emedicine, Google scholar, and Cochrane Library.

For the search were used the following key words: radiation therapy, intensity modulated radiation therapy, head cancer treatment, xerostomia, neck cancer treatment, dry mouth, salivary glands hypo-function, saliva reduction, saliva flow rate, low salivation, salivary gland sparing.

In this search were included: clinical studies, systematic reviews and qualitative studies. The survey was completed with online research of the mentioned data bases, with selection of the articles, while all articles were analyzed and the articles that met the needed criteria were extracted for following full review. From the total 87 articles that were selected with the online search, 41 articles were taken for detailed analysis about the studied topic; Intensity modulated radiation therapy and its influence on the salivary glands function.

Criteria for inclusion

For this study was applied protocol for defining the inclusion and exclusion criteria. The inclusion criteria for the evaluated articles were the following: studies that were done in vivo; articles that have analyzed strictly the use of IMRT technique; articles written in English; studies on patients with head and neck cancer; studies on patients with post- radiation induced xerostomia.

The exclusion criteria for analyzed articles were the following: surveys on patients with co-morbidity (such as metabolic alterations, diabetes mellitus, cardiovascular diseases and lupus erythematosus); studies made in vitro; studies relying only on presumptions about the consequences of IMRT technique as a new approach; studies that evaluate the effect of the radiation therapy combined with chemotherapy; studies on patients with xerostomia caused by other factors that are not post-radiation effects; studies on patients with systematic diseases; studies on patients with xerostomia as part of an autoimmune disease (Sjogren's syndrome), case reports and studies involving animals.

Extracted data were recorded into standardized database according to the following parameters: first author's surname, year of publication, number of patients, treatment details, xerostomia rates and clinical outcome.

Evaluation and results

In study done by Nutting C. M, Morden J. P, about 40% of patients resulted in suffering from symptoms of xerostomia after IMRT treatment [17]. The main difference with this parotid gland–sparing RT was in the following recovery of the glands over some period of time.

The damaged parotid gland has been shown that is capable of repairing its tissue and regaining some of its function in period of 2 years after the IMRT treatment which was different compared with the patients that were treated with conventional radiotherapy, what resulted in permanent xerostomia [17,18].

In the study by Nutting [17], after 12 months following of the treated patients, the side-effects such as xerostomia were reported in 73 of 82 total number of patients. Grade 2 or worse xerostomia has been proven that is significantly less occurred in the IMRT group (38%) than in the conventional radiotherapy group of patients (74%) [17,18].

From the results of the study done by Schmitt, C.et al [19], there were assessed 94 patients with head and neck cancer, that were treated with conventional radiotherapy or parotid-sparing IMRT therapy. The following period after the radiation treatment has been 24 months. After time of 2 years, 29% of the patients who were treated with IMRT were affected with xerostomia, compared with the other patients group that were treated with conventional radiotherapy 83% of patients were suffering from post-radiation effect xerostomia. Both forms of radiotherapy has been shown that led to xerostomia.

However, grade 2 xerostomia was much more rarely occurred in patients that were treated with the IMRT technique, compared to the other group treated with the conventional radiation therapy [19].

In the Eisbruch et al. [20] study, the parotid gland that has received a mean dose of radiation less than 26Gy, has recovered its' function and the salivary production levels one year after the radiation therapy.

Chao et al. [21] have suggested in order to spare the parotid gland, the mean dose of radiation to be with intensity of 32Gy in 50% of the parotid gland volume, so it could be able to recover its' salivary production. It has been shown that after a dose higher than 52Gy, after that there is permanent damage of the salivary gland [21,22].

Results from the survey conducted by Piet Dirix et al. [23], have shown that after 30 months following, the patients treated with IMRT therapy compared with the three-dimensional conformal radiotherapy treatment, IMRT resulted in significantly improved without recurrences survival of patients, without grade 3 or 4 toxicity in the patients treated with IMRT group, not acute or chronic. The use of IMRT technique has been shown that significantly reduces the incidence of acute and also the late side effects in patients, such as: mucositis, xerostomia, and dry-eye syndrome [23,24].

In other study with total number of 52 patients, all of them receiving intensity modulated radiation therapy with parotid glands sparing, 26 of the patients have also been spared the submandibular glands. The results of saliva flow and xerostomia have been recorded in 5 intervals (before IMRT, 2 months after, 6 months after, 12 months after and 18 months after the treatment). The radiation used was with intensity of 30 Gy in the first group of patients, and 57,4 Gy in the second group [25].

The results were taken after 2 and after 6 months, the level of xerostomia was significantly lower in patients with spared submandibular glands, however there was not big difference in the results for xerostomia levels gathered 12 and 18 months after the radiation therapy [25].

Pow et al. [26] have followed51 patients with nasopharyngeal carcinoma treated with conventional radiation therapy versus IMRT. Results have showed that 12 months after the treatment,83.3% of the patients in the IMRT group have recovered with 25% their salivary flow, compared to 9.3% of the patients inthe conventional group [26].

A similar study on patients with early stage nasopharyngeal cancer, 60 patients were treated with either conventional radiotherapy or parotid-sparing IMRT therapy. 1 year after the treatment, patients in theIMRT group had shown significantly smaller incidence of severe xerostomia, compared with patients in the conventional radiotherapy group (39.3 *vs* 82·1%; p = 0.01).

There was no difference in xerostomia reported from patients of the two groups [27].

In study with a total number of 56 patients suffering with oropharyngeal cancer, 30 patients were treated with IMRT, and the other 26 patients were treated with conventional radiation therapy. The gathered results have shown that, the mean dose of radiation to the parotid glands was 48.1 Gy for the conventional therapy, and 33.7 Gy for the IMRT treatment [28].

As a result, 6 weeks after treatment, the number of parotid flow complications was significantly lower after IMRT treatment (55%), compared with those after the conventional radiation therapy (87%). [28].

Study by Rij, C., Oughlane-Heemsbergen, W., Ackerstaff, A. *et al*, has shown that patients that were treated with IMRT technique stated that they had less opstructions while chewing and swallowing their food and that they didn't need much water during the day or night. Also in patients from IMRT group, the xerostomia scores have been much better for those with a dose lower than 26 Gy to the "spared" parotid gland. [29,30]

Discussion

Many studies so far have shown that the IMRT approach in radiation treatment offers big hope in reducing the radiation-caused xerostomia, by sparing the salivary glands in the radiation process, but without increasing the risk of recurrence the disease. Helical tomotherapy and computed tomography-based platform for IMRT has been shown that provides good covering of the target volume, while emitting the lowest doses to the salivary glands [31,32].

As in many studies was concluded that sparing all the salivary glands during IMRT by helical tomotherapy technique, when dose was strictly reduced to the parotid gland, submandibular gland and oral cavity, 61.3% of the patients that reported xerostomia as late consequence of the radiation treatment, has been restored to their normal level, 12 and 18 months after the IMRT radiotherapy also with following an early locoregional recurrence rate of 4% [32,33].

There is evidence that salivary gland cells are capable of proliferation meaning auto reparation, differentiation and also regenerating the damaged parts of their tissue. Recovery of the glands after radiation therapy is believed that is connected with the number of the remaining stem cells of the glands after the radiation treatment [34,35].

If there is also inclusion of the ducts in the radiation covered field during the process, it has been shown that it also leads to big loss of the regenerative capacity of the salivary gland, what in most of the cases results in long-term gland dysfunction with reduced saliva production and therefore xerostomia [36,37].

Authors suggest that the radiation dose to this region responsible for functional recovery should be reduced significantly using the IMRT method, what could play the main role in preventing the consequences such as xerostomia [38,39].

IMRT is currently considered to be a golden standard approach in head and neck cancer treatment, in addition to limit the cumulated radiation dose to the regional normal tissues.

IMRT is able to reduce maximally the dose to parotid, submandibular/sublingual and minor salivary glands, and with that to help maintain whole saliva flow rates and low the xerostomia effects [40].

Anyway, with all the benefits from the new approach IMRT in radiation therapy, the problem still is not solved totally, because in most of the cases, about 40% of patients are still suffering from xerostomia. Considering that, alternative options about treatment for xerostomia have to be taken in consideration.

There are many innovative approaches in the development of a topically administered medication that moisten the mouth and at the same time place an active ingredient locally to the affected salivary glands to protect them from irradiation and to neutralize the side effects [40].

In study performed by Palma LF, Gonnelli FA, Marcucci M. et al., saliva flow rate was measured after the treatment, patients were divided in control group (using standard sialometries) and test group of patients (using modified methods for saliva collection).

Results from unstimulated sialometries, have shown that the salivary flow rates of both groups ranged from 0 to 0.3 mL/min. The median of Control Group was 0.16 mL/min and the standard error was 0.0296 mL/min. And the median of Test Group was 0.1 mL/min and the standard error was 0.0307 mL/min [41].

Table 1. Results from latest studies about saliva flow rate in patients treated with IMRT

Author	Year	Improved saliva flow rate using IMRT	Not improved saliva flow rate using IMRT
Wang X.	2016	✓	
Acauan MD.	2015	✓	
Vissink A.	2010	✓	
Kaae JK.	2016		✓
Collan J.	2012	✓	
Hoyne C.	2017	✓	
Byungchul Ch.	2018	✓	
Rim CH.	2018	✓	
Schmitt C.	2011	✓	
Van Luijk P	2015		✓
Zhong-He W	2011	✓	
Kałużny J	2014	✓	
Teng F. et al	2019	✓	
A. Villa.	2015	✓	
Jaguar, G.C.	2017	✓	

Conclusion

Xerostomia still happens to be the most common issue that occurs in every patient treated with radiation therapy, but on the positive side is the fact that with using the approaches such as IMRT in the radiation treatment, the extent of xerostomia can be significantly minimized and controlled. In many cases have been proved that in some cases the salivary gland function can be partially restored after a few years, not totally but enough to improve the patient's life after the treatment.

References

1. Wang X, Eisbruch A. IMRT for head and neck cancer: reducing xerostomia and dysphagia. J Radiat Res. 2016;57 Suppl 1(Suppl 1):i69-i75.
2. Acauan MD, Figueiredo MA, Cherubini K, Gomes AP, Salum FG. Radiotherapy-induced salivary dysfunction: Structural changes, pathogenetic mechanisms and therapies. Arch Oral Biol. 2015;60:1802–10.
3. Vissink A, Mitchell JB, Baum BJ, et al. Clinical management of salivary gland hypofunction and xerostomia in head-and-neck cancer patients: successes and barriers. Int J Radiat Oncol Biol Phys. 2010;78(4):983-991.

4. Kaae JK, Stenfeldt L, Eriksen JG. Xerostomia after Radiotherapy for Oral and Oropharyngeal Cancer: Increasing Salivary Flow with Tasteless Sugar-free Chewing Gum. Front Oncol. 2016;6:111. Published 2016 May 3.
5. Strigari L, Benassi M, Arcangeli G, Bruzzaniti V, Giovinazzo G, Marucci L. A novel dose constraint to reduce xerostomia in head-and-neck cancer patients treated with intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys 2010; 77: 269– 76.
6. Hoyne C, BaAppSci (Medical Radiations),Marcus Dreosti, MBBS(Hons), FRANZCR,John Shakeshaft, MA, PhD& Siddartha Baxi,Comparison of treatment techniques for reduction in thesubmandibular gland dose: A retrospective study, J Med Radiat Sci64,2017;125–130.
7. Collan J, Kapanen M, Makitie A. Submandibular gland-sparing intensity modulated radiotherapy in the treatment of head and neck cancer: Sites of locoregional relapse and survival. Acta Oncol 2012; 51: 735– 42.
8. 8.Doornaert P, Verbakel W, Rietveld D, Slotman BJ, Senan S. Sparing the contralateral submandibular without compromising PTV coverage by using volumetric modulated arc therapy. Radiat Oncol 2011; 6: 74.
9. Murdoch-Kinch A, Kim HM, Vineberg KA, Ship JA, Eisbruch A. Dose-effect relationships for the submandibular salivary glands and implications for their sparing by intensity modulated radiotherapy. Int J Radiat Oncol Biol Phys 2008; 72: 373– 82.
10. Webster GJ, Rowbottom CG, Mackay RI. Accuracy and precision of an IGRT solution. Med Dosim 2009; 34: 99– 106.
11. Bertelsen A, Hansen CR, Johansen J, Brink C. Single arc volumetric modulated arc therapy of head and neck cancer. Radiother Oncol 2010; 95: 142– 8.
12. Vanetti E, Clivio A, Nicolini G, et al. Volumetric modulated arc radiotherapy for carcinomas of the oro-pharynx, hypo-pharynx and larynx: A treatment planning comparison with fixed field IMRT. Radiother Oncol 2009; 92: 111– 7.
13. Byungchul Ch.Intensity-modulated radiation therapy: a review with a physics perspectiveRadiat Oncol J. 2018 Mar.
14. Rim CH, Lee J, Kim WC, et al. A survey of radiation therapy utilization in Korea from 2010 to 2016: focusing on use of intensity-modulated radiation therapy. J Korean Med Sci. 2018;33:e67.
15. Das IJ, Cheng CW, Chopra KL, Mitra RK, Srivastava SP, Glatstein E. Intensity-modulated radiation therapy dose prescription, recording, and delivery: patterns of variability among institutions and treatment planning systems. J Natl Cancer Inst. 2008;100:300–7
16. Bhide SA, Ahmed M, Newbold K, Harrington KJ, Nutting CM. The role of intensity modulated radiotherapy in advanced oral cavity carcinoma. J Cancer Res Ther. 2012;8:67–71.
17. Nutting CM, Morden JP, Harrington KJ, Urbano TG, Bhide SA, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer(PARSPORT): a phase 3 multicentre randomised controlled trial. Lancet Oncol. 2011;12:127–36.
18. Dirix P, Vanstraelen B, Jorissen M, Vander Poorten V, Nuyts S. Intensity-modulated radiotherapy for sinonasal cancer: improved outcome compared to conventional radiotherapy. Int J Radiat Oncol Biol Phys. 2010;15:998–1004.
19. Schmitt, C. IMRT reduces incidence of xerostomia in patients with head and neck cancer. Nat Rev Clin Oncol 8, 194, 2011. https://doi.org/10.1038/nrclinonc. 2011.23.
20. Eisbruch A, Kim HM, Terrell JE, Marsh LH, Dawson LA, et al. Xerostomia and its predictors following parotid-sparing irradiation of head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2001;3:695–704.
21. Chao KS, Deasy JO, Markman J, Haynie J, Perez CA, et al. A prospective study of salivary function sparing in patients with head-and-neck cancers receiving intensity-modulated or three-dimensional radiation therapy: initial results. Int J Radiat Oncol Biol Phys. 2001;4:907–16.
22. Manikantan K, Khode S, Sayed SI et al. . Dysphagia in head and neck cancer. Cancer Treat Rev 2009;35:724–32.
23. Deasy JO, Moiseenko V, Marks L, Chao KS, Nam J, et al. Radiotherapy dose–volume effects on salivary gland function. Int J Radiat Oncol Biol Phys. 2010;76:58–63.

24. Van Luijk P, Pringle S, Deasy JO, Moiseenko VV, Faber H, et al. Sparing the region of the salivary gland containing stem cells preserves saliva production after radiotherapy for head and neck cancer. Sci Transl Med. 2015;16:305.
25. Zhong-He W. et al. Impact of salivary gland dosimetry on post-IMRT recovery of saliva output and xerostomia grade for head-and-neck cancer patients treated with or without contralateral submandibular gland sparing: a longitudinal study, Int J Radiat Oncol Biol Phys. 2011.
26. Pow EH, Kwong DL, McMillan AS, et al. Xerostomia andquality of life after intensity-modulated radiotherapy vsconventional radiotherapy for early-stage nasopharyngealcarcinoma: Initial report on a randomized controlled clinicaltrial.Int J Radiat Oncol Biol Phys 2006;66:981-91.
27. Kam MK, Leung SF, Zee B, et al. Prospective randomized studyof intensity-modulated radiotherapy on salivary gland functionin early-stage nasopharyngeal carcinoma patients. J Clin Oncol2007;25:4873-79.
28. Pètra M.BraamM.D.Chris H.J.Terhaard, Intensity Modulated therapy significantly reduces xerostomia compared with conventional radiotherapy, International Journal of Radiation Oncology, Biology, Physics, vol. 66. Issue 4, November 2006, 975-980.
29. Rij, C., Oughlane-Heemsbergen, W., Ackerstaff, A. et al. Parotid gland sparing IMRT for head and neck cancer improves xerostomia related quality of life. Radiat Oncol 3, 41, 2008.
30. Kałużny J, Wierzbicka M, Nogala H, Milecki P, Kopeć T. Radiotherapy induced xerostomia: mechanisms, diagnostics, prevention and treatment--evidence based up to 2013. Otolaryngol Pol. 2014;68:1–14.
31. Teng F. et al. "Reducing Xerostomia by Comprehensive Protection of Salivary Glands in Intensity-Modulated Radiation Therapy with Helical Tomotherapy Technique for Head-and-Neck Cancer Patients: A Prospective Observational Study." BioMed Research International 2019.
32. A. Villa, A. Wolff, D. Aframian et al., "World Workshop on Oral Medicine VI: a systematic review of medication-induced salivary gland dysfunction: prevalence, diagnosis, and treatment," Clinical Oral Investigations, vol. 19, no. 7, pp. 1563–1580, 2015.
33. J. Castelli, A. Simon, G. Louvel et al., "Impact of head and neck cancer adaptive radiotherapy to spare the parotid glands and decrease the risk of xerostomia," Journal of Radiation Oncology, vol. 10, no. 1, article no. 6, 2015.
34. Jaguar, G.C., Prado, J.D., Campanhã, D. et al. Clinical features and preventive therapies of radiation-induced xerostomia in head and neck cancer patient: a literature review. Appl Cancer Res 37, 31, 2017.
35. Verrone JR, Alves FA, Prado JD, Marcicano AD, de Assis Pellizzon AC, Damascena AS, Jaguar GC. Benefits of an 649 intraoral stent in decreasing the irradiation dose to oral healthy tissue: dosimetric and clinical features. Oral Surg Oral Med Oral Pathol Oral Radiol. 2014;118:573–8.
36. Sood AJ, Fox NF, O'Connell BP, Lovelace TL, Nguyen SA, et al. Salivary gland transfer to prevent radiation-induced xerostomia: a systematic review and meta-analysis. Oral Oncol. 2014;50:77–83.
37. Yang WF, Liao GQ, Hakim SG, Ouyang DQ, Ringash J, et al. Is Pilocarpine Effective in Preventing Radiation-Induced Xerostomia? A Systematic Review and Meta-analysis. Int J Radiat Oncol Biol Phys. 2016;94:503–11.
38. Vigneswaran N., Williams M.D. Epidemiological Trends in Head and Neck Cancer and Aids in Diagnosis Changing Epidemiology of Head and Neck Cancer. Oral Maxillofac. Surg. Clin. N. Am. 2014;26:123–141.
39. Osailan S, Pramanik R, Shirodaria S, Challacombe SJ, Proctor GB. Investigating the relationship between hyposalivation and mucosal wetness. Oral Dis. 2010
40. Jensen SB, Pedersen AML, Vissink A, et al. A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: management strategies and economic impact. Support Care Cancer. 2010 Mar 25.
41. Palma LF, Gonnelli FA, Marcucci M, Giordani AJ, Dias RS, Segreto RA, et al. A novel method to evaluate salivary flow rates of head and neck cancer patients after radiotherapy: a pilot study. Braz J Otorhinolaryngol. 2018;84:227-31.