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Original article

EVALUATION OF SALIVARY HYPOFUNCTION AND ORAL COMPLICATION AFTER RADIOTHERAPY IN PATIENTS WITH MALIGNANT NEOPLASMS OF HEAD AND NECK

ЕВАЛУАЦИЈА НА САЛИВАРНА ХИПОФУНКЦИЈА И ОРАЛНИ КОМПЛИКАЦИИ ПОСЛЕ РАДИОТЕРАПИЈА КАЈ ПАЦИЕНТИ СО МАЛИГНИ НЕОПЛАЗМИ НА ГЛАВА И ВРАТ

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Abstract

Introduction. In patients with head and neck malignant neoplasms salivary glands are affected by the radiation therapy because they are located close to the place that is exposed to the total dose of radiation. Therefore, xerostomia and dysphagia are the most frequent post-radiation complications that affect the life of these patients. The volumetric modulated radiation therapy enables higher doses of radiation to be focused on the targeted place, and the surrounding healthy tissues to be exposed to the harmful effect of radiation as less as possible.

Method. This study was conducted by cooperation of the University Clinic for Radiotherapy and Oncology and University Clinic of Maxillofacial Surgery-Skopje. The study sample consisted of 30 patients treated with one of the radiation techniques: 3DCRT and VMAT. The stimulated salivary flow from parotid glands was defined using modified Lashley cups. Post-radiation xerostomia and mucositis were noted in grades based on the clinical examination, and the rest of the post-radiation complications during the first control after the radiation therapy were registered if they appeared. The moisture of oral cavity was evaluated by the modified Schirmer method.

Results. The comparison of patients treated with one of the radiation techniques showed significantly larger amount of produced stimulated saliva (ml/min) in patients treated with VMAT compared to those treated with 3DCRT ($p=0,0054$). An insignificant linear negative correlation was found between the volume of stimulated salivary flow (ml/min) and the localization of the malignant neoplasm-salivary flow was insignificantly decreased in patients with malignant neoplasm of the nasopharynx, oropharynx, hypopharynx and larynx

($R_{(30)}=-0,151$; $p=0,4602$). The mucositis appearance was significantly associated with the use of 3DCRT method. The low grade of xerostomia was significantly associated with the use of VMAT method.

Conclusion. The use of the new technique, volumetric modulated radiation therapy, enables to spare the salivary function that is proved by the increased salivary flow, the decreased level of xerostomia and the decreased representation of all other post-radiation complications.

Keywords: hyposalivation, xerostomia, malignant neoplasm of head and neck, volumetric modulated radiation therapy, irradiation consequences

Апстракт

Вовед. Кај пациенти со малигни неоплазми на глава и врат, терапијата со радијација несомнено ги афектира саливарните жлезди од едноставна причина што тие се наоѓаат во близина на местото каде што се дистрибуира тоталната доза на радијација. Последователно на тоа ксеростомијата и дисфагијата се најчестите пострадијациони компликации кои го нарушуваат квалитетот на живот на овие пациенти. Волуметриски модулираната радиотерапија овозможува повисоките дози на радијација да бидат фокусирани на целното место, а околните здрави ткива да бидат колку е можно помалку изложени на штетното дејство од радијацијата.

Методи. Истражувањето се заснова на соработка помеѓу Универзитетската клиника за радиотерапија и онкологија и Универзитетската клиника за максилороцијалнахирургија-Скопје. Истажувачкиот примерок вклучува 30 пациенти третирани со една од техниките на радиотерапија: 3DCRT и VMAT. Стимулираниот саливарен проток од паротидни жлезди се одредуваше со помош на модифицирани Lashley cups. Пострадијационата ксеростомија и мукозитис се евидентираше во степени врз

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основа на клиничкиот преглед, а сите други пост-радијациони компликации за време на првата контрола после завршена радиотерапија, се евидентираа со присуство и отсуство на истите. Мерењето на влажноста на оралната празнина се изведуваше со помош на модифицирана Schirmer метода.

Резултати. Споредбата на пациентите третирани со една од двете техники на радиотерапија укажува на сигнификантно поголема количина на излучена стимулирана слива (ml/min) кај пациентите третирани со VMAT споредено со 3D CRT ($p=0,0054$). Помеѓу количина на стимулиран саливарен проток (ml/min) и локализацијата на малигна неоплазма утврдена беше несигнификантна линеарна негативна корелација-саливарниот проток несигнификантно се намалуваше кај пациентите со малигном на Nasopharynx, Oropharynx, Hypopharynx, Larynx ($R_{(30)} = -0,151$; $p=0,4602$). Од двете методи, појавата на оралниот мукозитис сигнификантно асоцираше со методот 3DCRT. Слабиот степен на ксеростомија сигнификантно асоцираше со методот VMAT. **Заклучок.** Примената на новата техника на волуметриски модулирана радиотерапија овозможува да се зачува саливарната функција кое се докажува преку зголемениот саливарен проток, а намален степен на ксеростомија и намалена застапеност на сите пострадијациони компликации.

Клучни зборови: хипосаливација, ксеростомија, малигни неоплазми на глава и врат, волуметриски модулирана зрачна терапија, ирадијациони последици

Introduction

The therapy in patients with malignant head and neck neoplasm that consists of radiation inevitably affects salivary glands and their surroundings; therefore patients face negative consequences such as progressive malfunction of salivary glands, followed by a significant level of xerostomia (Figure 1). Despite all of the efforts to protect the surrounding tissues from damaging during the radiation treatment, salivary glands are still exposed to the radiation due to their close location to the exposed area [1]. Having this in mind, xerostomia in most of the cases is the main cause of the symptoms: oral mucositis, changes in oral microflora, dysphagia, throat inflammations, changes or loss of the taste, caries, changes in the voice quality, halitosis, discomfort, problems with chewing and swallowing, which lead to nutritive complications and loss of weight in the future [2,3].



Fig. 1. Dry mouth – xerostomia

Salivary gland impairment due to radiation therapy happens in 4 different phases: the first phase happens from the 1st to the 10th day, when the water component in the tissue is being eliminated, but the acinar cells and amylase secretion are not being affected; the second phase takes place from the 10th to the 120th day, acinar cells are exposed to membrane degeneration and they also lose their ability to produce amylase; the third phase is from the 120th to the 240th day, known as a phase of belated toxicity characterized by losing the function of acinar cells as a result of stem cells loss; the fourth phase is known as a regenerative phase, however the deterioration of the salivary gland function is still continuing in this phase as a result of the nerves damaging used for glands ducts and blood vessels [4,5].

3DCRT-Three-Dimensional Conformal Radiation Therapy (3DCRT) and Volumetric Intensity Modulated Arc Therapy (VMAT) are two different techniques that are aimed at providing a precise and efficient treatment for patients with malignant neoplasms (Figure 2). Three-dimensional conformal radiation therapy is a standard technique that enables a good view of the anatomic structures and radiation beams in three dimensions. The segments for radiation treatment can be modified individually according to the shape of the tumor. On the other hand, the volumetric modulated radiation therapy is considered to be innovative and advanced technique that offers modulation of the radiation intensity in small multiple parts; therefore, this method enables higher doses of radiation to be focused on the targeted place, while the surrounding healthy tissues are exposed to the harmful effects of radiation as less as possible. Recent studies have been focused to prove that the new approach of modified radiation therapy (volumetric modulated radiation therapy-VMAT) is expected to reduce the xerostomia incidence, and subsequently to improve the quality of patients' life that have been treated with this method of radiation therapy [6,7].

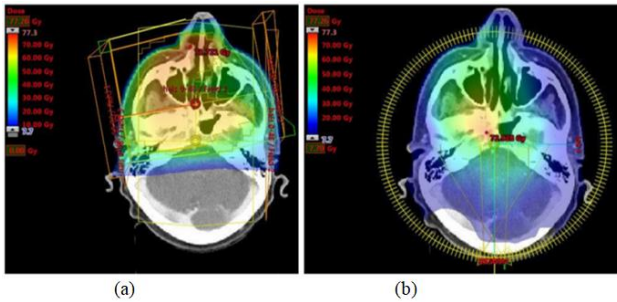


Fig. 2. Comparison between three-dimensional conformal radiation therapy (a) and volumetric modulated radiation therapy (b)

Aim

The main aim of this study was to evaluate the salivary hypofunction by determining the parotid stimulated salivary flow and assessment of the oral complications in patients with malignant neoplasms of the head and neck, treated with three-dimensional conformal radiation therapy and volumetric modulated radiation therapy.

Material and methods

The study sample consisted of 30 patients treated with one or both techniques of radiation therapy: 3DCRT or VMAT. Taking into consideration in advance defined exclusion and inclusion criteria, patients treated with one of the techniques of radiation therapy at the University Clinic for Radiotherapy and Oncology in

Skopje were included in the study. The clinical examination involving the measurement of stimulated salivary flow and moisture of oral cavity was performed at the University Clinic of Maxillofacial Surgery with previously obtained patients' written consent. Salivary flow measurement and post-radiation complications were done immediately after the first assessment of the finished radiation therapy. Xerostomia and oral mucositis were noted in grades; however, the rest of the post-radiation complications were noted only if they appeared. Stimulated saliva from the parotid glands was collected using special devices made in line with the modified Lashley cups principle, and they were made by dental laboratory technicians, using silicone mass for duplication and connecting it with a tube system that allows collection of saliva from both parotid glands at the same time. The device is being placed in the upper vestibule where the salivary duct of parotid gland is located, and is fixed by using vacuum. Saliva from the duct flows in the oval part of the device from where it is being moved through the tube system saliva and collected in microliters graduated syringe. The obtained values are being divided by the minutes spent in saliva collection to define the salivary flow in one minute. In order to gather stimulated saliva, stimulation was done by using citric acid applied on a cotton applicator and placed on the dorsum part of the tongue, specifically on the dorso-lateral edges of the tongue, five times in duration of 2 minutes (Figure 3).

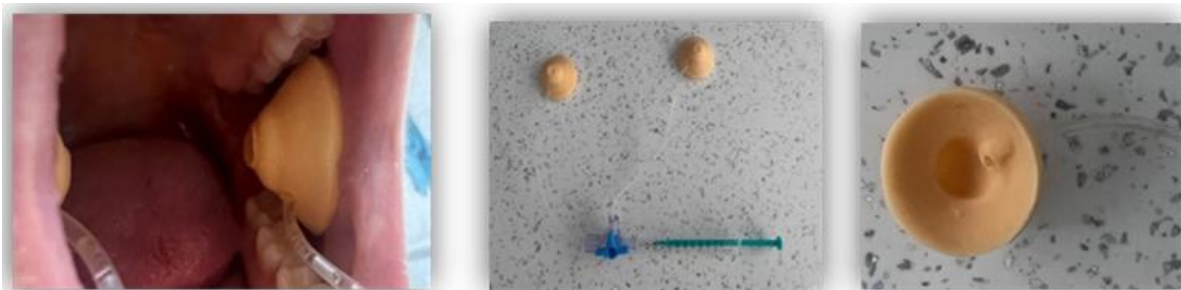


Fig. 3. Modified Lashley cups

By using the modified Schirmer method for measurement of the moisture in the oral cavity, Schirmer stripes are applied at the bottom of the oral cavity of a patient, and the results are available 3 minutes later (Figure 4). The obtained results are noted immediately; the stripes are divided in millimeters starting with 5 mm to 35 mm. If the observed result was lower than 5 mm, we considered it as value 5. The results were registered from the size of wet zone on the stripes in millimeters, that can be easily seen as a darker part.

According to Primary site of malignant neoplasm classification, patients were divided in two large groups. The first group was consisted of patients with malignant neoplasm located on the: lip, oral cavity, tongue, floor of the mouth, buccal mucosa, retromolar fossa, hard

palate, maxilla and mandible. The second group was consisted of patients with malignant neoplasm located on the: nasopharynx, oropharynx, hypopharynx and larynx.



Fig. 4. Modified method for measuring mouth moisture

Results

The evaluation of patients with malignant neoplasm located on the lip and oral cavity treated with different methods showed a significantly higher volume of stimulated saliva (ml/min) in patients treated with the

VMAT compared to those treated with the 3DCRT technique (p=0.0054).

Patients with malignant neoplasm of the nasopharynx, oropharynx, hypopharynx and larynx, treated with the VMAT method showed insignificantly bigger volume of produced saliva (ml/min) compared to those treated with the 3DCRT method (p=0.0588) (Table 1).

Table 1. Comparison of saliva (ml/min) between 2 groups of participants

Parameters	N	Mean± SD	Min / Max	Median (IQR)	p
<i>Saliva (ml/min) - Lip, Oral cavity (tongue, floor of the mouth, buccal mucosa, retromolar fossa, hard palate, maxilla, mandible)</i>					
VMAT	8	0.21±0.09	0.08/0.30	0.23(0.14-0.30)	Z=2.781
3DCRT	7	0.06±0.01	0.05/0.08	0.06(0.06-0.07)	p=0.0054*
<i>Saliva (ml/min) - Nasopharynx, Oropharynx, Hypopharynx, Larynx</i>					
VMAT	7	0.19±0.11	0.06/0.30	0.21(0.10-0.29)	Z=-1.889
3DCRT	8	0.07±0.02	0.05/0.11	0.08(0.05-0.09)	p=0.0588

SD-standard deviation, IQR-Interquartile range, *significant for p<0.05

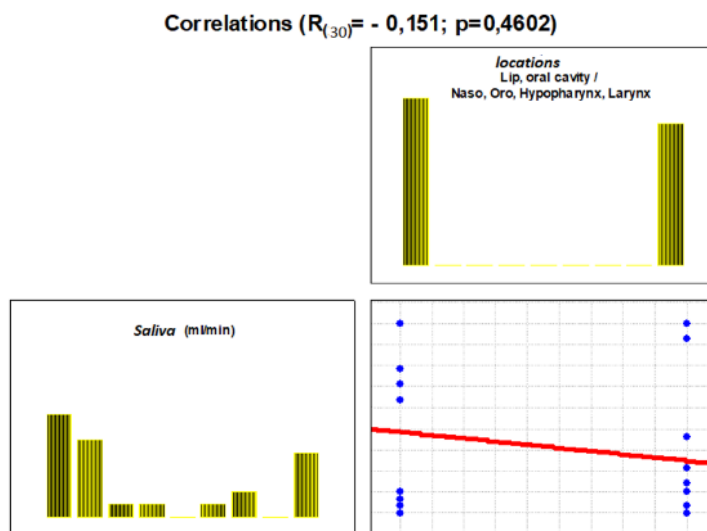


Fig. 5. Correlation between stimulated salivary flow and malignant neoplasm localization

There was an insignificantly linear negative correlation between stimulated salivary flow (ml/min) and malignant neoplasm localization-salivary flow insignificantly decreased in patients with malignant neoplasm

of the nasopharynx, oropharynx, hypopharynx, and larynx

($R_{(30)} = -0,151; p = 0,4602$) (Fig.1a)

Table 2. Distribution of post-radiation complications

Post-radiation complications	3DCRT (n=15)	VMAT (n=15)	Total (n=30)	p
grade 1- mild	2(16.66%)	9(75%)	11(45.83%)	p=0.0123*
grade 2 - moderate	8(66.67%)	3(25%)	11(45.83%)	p=0.0996
grade 3 - severe	2(16.66%)	0(0%)	2(8.34%)	-
grade 4- disabling; life threatening	0(0%)	0(0%)	0(0%)	-

Fisher Exact test, *significant for, p<0.05

Mucositis as a complication after treatment was significantly associated with using the 3DCRT method for radiation therapy. The emerge of the other post-radiation complications (difficulties in mastication,

dysphagia, dysgeusia and dysphonia) was not associated with any of the methods used for radiation treatment (3DCRT/VMAT) (Table 2).

Table 3. Distribution of xerostomia grades

Xerostomia grading scale - NCI CTCAE	3DCRT (n=15)	VMAT (n=15)	Total (n=30)	p
Oral mucositis	10(83.3%)	4(33.3%)	14(58.3%)	p=0.0384*
Difficult mastication	11(91.6%)	7(58.3%)	18(75%)	p=0.1573
Dysphagia	11(91.6%)	7(58.3%)	18(75%)	p=0.1573
Dysgeusia	11(91.6%)	6(50%)	17(70.8%)	p=0.0724
Dysphonia	9(75%)	5(41.6%)	14(58.3%)	P=0.2149

Fisher Exact test, *significant for, $p < 0,05$

The low level of xerostomia was associated significantly with the usage of the VMAT method. The moderate level of xerostomia was found in borderline association with the 3DCRT method. The severe level of xerostomia was found only in 2 patients treated with the 3DCRT method, and in none of patients treated with the VMAT method. Disabling xerostomia was not registered in any of the examined patients in the study (Table 3).

The results obtained by using the modified Schirmer

test were as follows: the average value of produced saliva volume in patients treated with the three-dimensional conformal radiation therapy was 4.2 mm; modus 1 and 0; median 3.5; maximal value was 9 mm and minimal was 0 mm; standard deviation 1.0. In the second group of patients treated with the volumetric modulated radiation therapy, the mean value was 5.5 mm; modus 2; median 6; maximal 12 mm and minimal value was 0.2 mm; standard deviation was 0.4 (Table 4).

Table 4. Average values of collected saliva using the modified Schirmer test measured in mm

Type of radiation therapy	Mean	Modus	Median	Max	Min	SD
3DCRT	4.2	1; 0	3.5	9	0	1.0
VMAT	5.5	2	6	12	0.2	0.4

Discussion

During the radiation process it is necessary to protect the salivary gland function from the damaging effects of the radiation. Protection of the submandibular Salivary glands during radiation is more complicated compared to that of the parotid glands due to their location that is in the same place as the affected lymphatic nodes. The use of volumetric modulated radiation therapy is based on computer controlled linear accelerators that apply the radiation doses precisely on the place that is specified for radiation or more precisely where the tissue is affected by the tumor [7,8].

By introducing the new method of volumetric modulated radiation therapy (VMAT), xerostomia that appears after radiation treatment in patients is significantly reduced, which also contributes to improving the quality of life in patients treated with radiation therapy [9,10]. The study by Taoran C. *et al.* evaluated a total of 222 patients treated with IMRT and VMAT radiation therapy, and were followed in a period of 23 months and 7 months. The results obtained by using the VMAT showed significant improvement that resulted in significantly lower grades of second-degree dysphagia and xerostomia in patients after the received radiation therapy [11,12].

Nutting C M, Morden JP. found that 4% of their study participants suffered of a post-radiation xerostomia after

treatment with the VMAT. The main difference in the approach with sparing the parotid glands during treatment had been in the following period of regeneration of the parotid glands. The damaged parotid glands showed the ability of regeneration to some degree in a 2-year period after the VMAT treatment, which compared to xerostomia in patients treated with the conventional radiation therapy proved to be permanent. After 12 months following the treated patients, xerostomia was registered in 73% of the total number of participants (82). Severe xerostomia was proved to be significantly rare in the group of participants treated with the intensity modulated radiation therapy (38%), compared to the group of patients treated with the conventional radiation therapy where the result was 74% [13,14]. According to Chris Nutting, the modified radiation therapy VMAT needs to be taken and applied as a golden standard in patients with high risk of radiation-related xerostomia [13]. Chottetanaprasith in his evaluation of 33 patients treated with VMAT presented results showing that survival rate at 3 years after treatment was 81%; acute symptoms as a result of the therapy were mucositis in 36% of participants, first grade xerostomia in 57.6%, and second grade xerostomia in 24.2% of participants. A conclusion was derived that using the VMAT approach in treating patients with nasopharyngeal carcinoma was acceptable and it offered good results with high survival rate and acceptable negative consequences [15].

Conclusion

In conclusion, the usage of the new technique-volumetric modulated radiation therapy-offers sparing of the salivary glands function, which can be proved with the increased salivary flow, decreased grade of xerostomia and decreased representation of all post-radiation complications compared to patients treated with the three-dimensional conformal radiation therapy.

Conflict of interest statement. None declared.

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