Research Article
Cancer Research and Cellular Therapeutics

Title: **Evaluating the Upper and Lower Lip as Critical Organs in Radiotherapy for Head and Neck Cancer Patients.**

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Abstract:
Squamous cell carcinoma of the head and neck is condition associated with a poor prognosis. Current treatment methods are a combination of various techniques. Reactions after radiotherapy, particularly those affecting mucous tissues such as the lips, are a major issue after radiotherapy.
This study aimed to assess the doses deposited on the lip area, considering its proximity to target areas during radiotherapy. Study was conducted on 100 patients with diagnosed head and neck cancers. These patients were treated with radiotherapy, sometimes combined with chemotherapy, and for some, it was postoperative treatment. The minimum, average, and maximum doses deposited on the lip area were assessed, divided into group I (neck) and group II (head). The lowest doses were observed in the larynx area, and the highest in the oral cavity (67.7% of the dose from 70 Gy and 76.46% from the minimum dose).
Patients were further divided based on treatment methods, with the highest maximum lip dose found in those undergoing postoperative radiochemotherapy (Dmax 42.34Gy). Post-radiation reactions were then analyzed, showing higher reactions (lowest, average, and maximum) in group II (head area). Tumor location analysis showed the lowest maximum reaction according to the Dische classification in the larynx and other locations, and the highest in the pharynx. Postoperative patients with adjuvant radiochemotherapy had the highest minimal and maximum reactions.
Despite the lack of statistical significance, the results suggest the importance of contouring the lips as a critical organ to reduce radiation reactions, potentially improving patients' quality of life.
Key words: radiotherapy; cancer; lip; head; neck

1. Introduction:

Head and Neck Squamous Cell Carcinoma refers to tumors located in the mucosa of the upper part of the respiratory and digestive systems (oral cavity, pharynx, larynx, nasal cavity, salivary glands, paranasal sinuses). These tumors share similar diagnostic and therapeutic issues, although they differ in their clinical course and prognosis and constitute a serious medical problem [1]. A major form of treatment is radiotherapy, which is the therapeutic use of ionizing radiation to sterilize or depopulate the number of cancerous cells. The basic advantage of the radiotherapy is its sparing nature, compared to more invasive surgical treatment and it is the treatment of choice in early stages of, among others, pharyngeal and laryngeal cancer [2,3]. The effect of radiation is not limited to the tumor itself, but also extends to the surrounding healthy tissues, initiating cascades of physical, chemical and biochemical processes, which then lead to biological effects, causing various clinical symptoms, including post-radiation side effects.
During radiotherapy of head and neck cancers, the oral cavity is in the radiation field. The oral cavity, including the lips, is the initial part of the digestive tract, which performs many organic functions, such as breathing, eating, drinking and articulation. Its function is to facilitate food intake, sucking breast milk in infants and preparing portions of food in the mouth in adults. The presence of the lips prevents, among other things, liquids and food from falling out of the mouth, as well as the leakage of saliva from the mouth. The movements of the tongue, soft palate and lips process the sounds produced on the vocal folds of the larynx, thus enabling the pronunciation of specific sounds. When it is not possible to inhale through the nose, the oral cavity supports the respiratory system and is an alternative route for the respiratory tract [4].

The outer surface of the lip is covered with skin and the internal part with mucous membrane that extends to the gums. The lips lack hair and sweat glands, but there are sebaceous glands, whose secretions protects them from drying out. The lips form a space called the vestibule of the mouth together with the cheeks, the external surfaces of the teeth and the alveolar ridges covered by the gums. Small salivary glands located in the lips and cheeks drain secretions into the vestibule of the oral cavity [4].
The side effects of radiation can last weeks, months or even years after the treatment. The risk of damage to healthy tissues increases when radiotherapy is combined with chemotherapy, as the use of chemotherapy may be additive and/or synergistic. Side effects are distinguished based on their timing and can be divided into early side effects and late side effects. Another classification is based on the extent of post-radiation reactions, dividing them into local and systemic reactions. During radiotherapy of head and neck cancers, the symptoms associated with acute radiation damage to the mucous membranes, which depend on the so-called functional reserve and spatial structure are major side effects. Chewing and swallowing disorders are the consequence of acute radiation reaction as well as xerostomia. When mucosal defects appear, affecting the entire thickness of the epithelium, painful symptoms occur over a large area of the mucosa, and the risk of bacterial and fungal infection increases [3].
High post-irradiation reaction of the oral cavity can have serious consequences, because it significantly worsens the patient's comfort, leads to weight loss, necessitates the inclusion of intensive pharmacological treatment (anti-oedematous, analgesic, antibacterial, antifungal, intravenous hydration). It might even require the usage of PEG, which may lead to a pause in radiotherapy treatment or even its premature termination. Failure to administer the full therapeutic dose of both radiotherapy

and to complete all planned cycles of chemotherapy in the case of combined treatment significantly reduces the chances of recovery, and thus worsens the prognosis for the patient [1,2].
The risk of occurrence, intensity and nature of early and late radiation side effects depend on many external factors that determine the response of healthy tissues to ionizing radiation. The size of the surface of the irradiated epithelium plays a major role- the larger the area, the more severe the functional symptoms are, the worse the reaction tolerance is for the patient and the longer the healing process is. In addition to physical parameters, some biological factors also affect the course of the reaction. These include related factors with radiotherapy, the patient and cancer [5,6,7]. Factors related to radiation therapy include: type and energy of radiation, total dose administered, fractional dose and duration of treatment. The volume of healthy tissues exposed to high doses of radiation is also important: larger volumes increase the risk of organ dysfunction [7,8].

2. Purpose of the study:

The aim of the study was to assess the radiation doses deposited on the volume of the upper and lower lip, analyze radiation reactions and the consider therapeutic areas for various locations of head and neck cancers.

3. Material and Methods:

Retrospective study carried out at the Department of Oncology, Faculty of Health Sciences, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń. It was planned on a group of 100 patients with cancers of the head and neck region, after obtaining the consent of the Bioethics Committee at the Nicolaus Copernicus University in Toruń Collegium Medicum in Bydgoszcz No. KB 150/2022. Each patient was treated according to accepted standards of therapeutic procedure.
The study involved patients with head and neck cancers who were qualified for standalone radical radiotherapy or radiochemotherapy.
During the study, the following data were verified and analyzed: maximum, minimum and average doses deposited on the lips and oral mucosa, assessment of the correlation between doses deposited on the lips and: radiation reaction; administered dose of radiation; and the location of the irradiated area.
The results of the study were used to prepare an analysis on the usefulness of the aforamentioned method, to determine the dose deposited in the critical organ, depending on the location of the primary disease and the impact on the monitoring of radiation reactions in patients with head and neck cancer. Consequently, this usefulness for therapeutic purposes in patients, including modifying treatment plans and improving the quality of therapeutic procedures to spare this critical organ, as well as improving the quality of the patient's functioning during and after radiotherapy was evaluated.

4.1 Patients group:

The study was conducted in a group of 100 patients qualified for radiotherapy of head and neck cancers. All patients were patients of the Radiotherapy Department of the Oncology Center in Bydgoszcz in the period from 2017 to 2021. Postoperative treatment was performed in 52 patients. In 54 patients, combined treatment involving chemotherapy and radiotherapy was used, while in 46 patients radiotherapy was used as a standalone treatment.

4.2 Diagnostic:

The examination was performer using CT scans, and/or PET-CT, and/or Magnetic Resonance Imagining for treatment planning. In these scans, the target areas, critical organs, and upper and lower lips were delineated in patients with head and neck cancers. Each patient underwent weekly laryngological check-ups during radiotherapeutic treatment in order to classify and record the severity of the acute radiation reaction according to the Disch scale. Appropriate pharmacological treatment was initiated based on the severity of the acute radiation reaction [3].
The patients were divided into two groups depending on the location: group I – primary tumors located in the neck, group II - tumors located in the head. Subsequently, the patients were divided into groups based on specific locations, such as: pharynx, larynx, oral cavity, and other locations. The values of maximum, minimum and average doses as well as the volume of the risk area for the upper and lower lip were assessed based on the analysis of the DVH histogram.

4.3 Statistics analysis:

The analysis was performed using Student's T-distribution and Pearson's r-correlation coefficient. Statistical significance was assumed at $p<0.05$.

4.4 Descriptive statistics:

The study was conducted on a retrospective group of 100 patients with cancer of the head and neck region treated radically. Of these patients, 74 (74%) were men and 26 (26%) were women, with the average age at the completion of radiotherapeutic treatment being 63 years old. The youngest patient was 35 years old and the oldest was 85 years old.
In the entire group, surgical treatment was performed in case of 48 (48%) patients. All patients (100%) underwent radiotherapy and 54 (54%) received it in combination with chemotherapy.
In terms of location, patients were divided into two groups - a group of tumors located in the cervical part (Group I) and a group of tumors located in the head area (Group II). In the first group there were 44 (88%) patients with laryngeal tumors and 6 (12%) with other localizations in this area. In the second group there were 29 (58%) patients with pharyngeal cancer, 18 (36%) patients with an oral lesion, and 3 (6%) patients with other locations (Fig. 1), (Tab. 1).

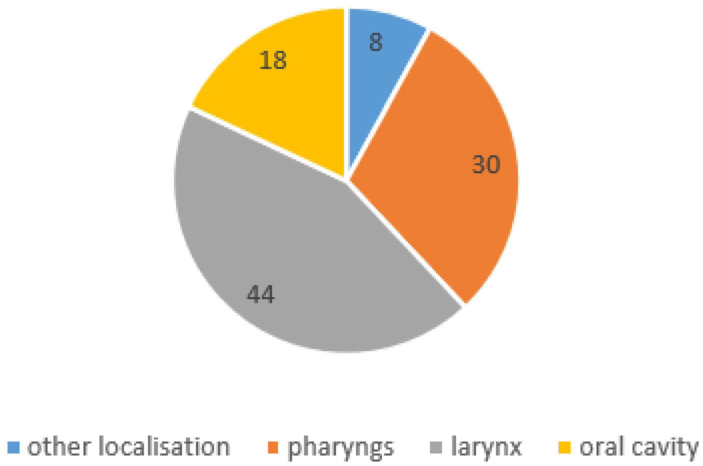

Figure 1- Distribution of patients based on tumor location

Gender::	Male 74 (74%) Female 26 (26%)
Age:	63 on average (35-85)
Localisation:	Pharyngs 30 (30%) Larynx 44 (44%) Oral cavity 18 (18%) Other localisations 8 (8%)
Operation:	Operated 48 (48%) Without operation 52 (52%)
Form of therapy:	Standalone radiotherapy 46 (46%) Radiochemotherapy 54 (54%)

Table 1- Patients characteristics

In the next step, the minimum doses, average doses and maximum doses deposited in the area were assessed:

- **PTV1 (Planning Target Volume)**, i.e., the tumor area and/or the area of subclinical disease, the so-called area of highest risk of spreading the disease;
- **PTV2**, an area of intermediate risk of spreading the disease;
- **PTV3** so-called an elective area, i.e., an area of low risk of spreading the disease.

The lowest deposited dose during radiotherapy was 54Gy, the highest 74Gy, with the average dose (PTV1 68.48Gy; PTV2 65Gy; PTV3 62Gy), and the number of fractions ranged from 20 to 37 (Fig. 2).

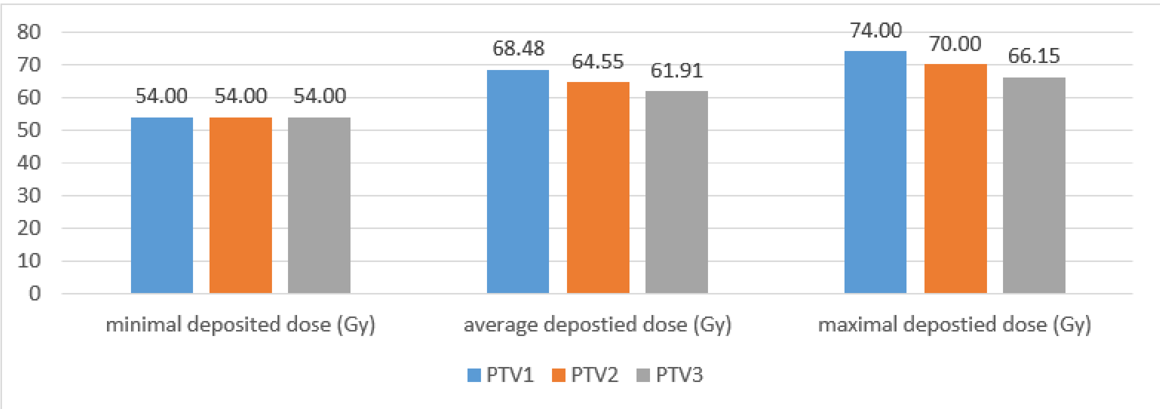

Figure 2- Patient characteristics - radiotherapy planning

4.5 Analysis of the results for the upper and lower lip:

In this part of the study, lip data was analyzed, including the minimum; average and maximum dose; as well as lip volume (Tab. 2).

Minimal lip volume (cm^3)	3,5
Average lip volume (cm^3)	11,57
Maximal lip volume (cm3)	19,8
Minimal cumulative dose on lip area (Gy)	0,01
Average cumulative dose on lip area (Gy)	25,46
Maximal cumulative dose on lip area (Gy)	73,34

Table 2- General characteristics for the upper and lower lip

Then, the same parameters were assessed for group I (cervical location) and group II (head location). The average maximum dose to the lip area differed between the first and second groups and was higher for the cervical location 40.9Gy vs. 34Gy (16.88% difference), a similar trend was observed between the groups for the average dose, where the dose was higher for group I and was 25.46Gy vs. 19.83Gy for group II - head location (22.11% difference).

Contrary to these results, the mean minimum dose to the lip area was higher in group II (head) compared to group I (neck) and was 16.72Gy vs. 10.62Gy (36.48% difference) (Fig. 3).

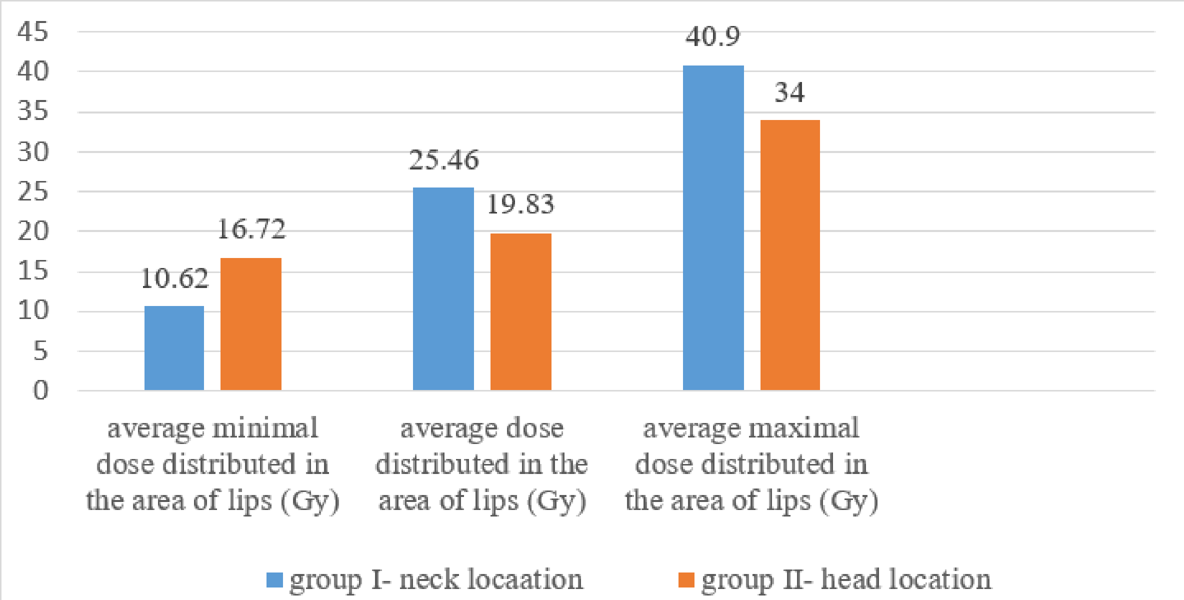

Figure 3- Comparison of average dose distributions in the area of the upper and lower lip in group I - neck location and in group II - head location

In the subsequent part of the study, the same parameters were assessed, i.e., the minimum, average and the maximum dose deposited on the lip area based on the location of the cancer. All the above parameters were the lowest for localization within the larynx, while the highest doses (average and maximum) the area of the upper and lower lip were administered during radiotherapy of oral cancer, where the maximum dose to the lips was 47.39 Gy, which was 67.7% of the 70 Gy administered during radiotherapy and 76.46% of the minimum dose administered. The average minimum dose was the highest for other locations and totaled 19.59Gy, which was 31.69% of the minimum average dose for this location (Fig. 4).

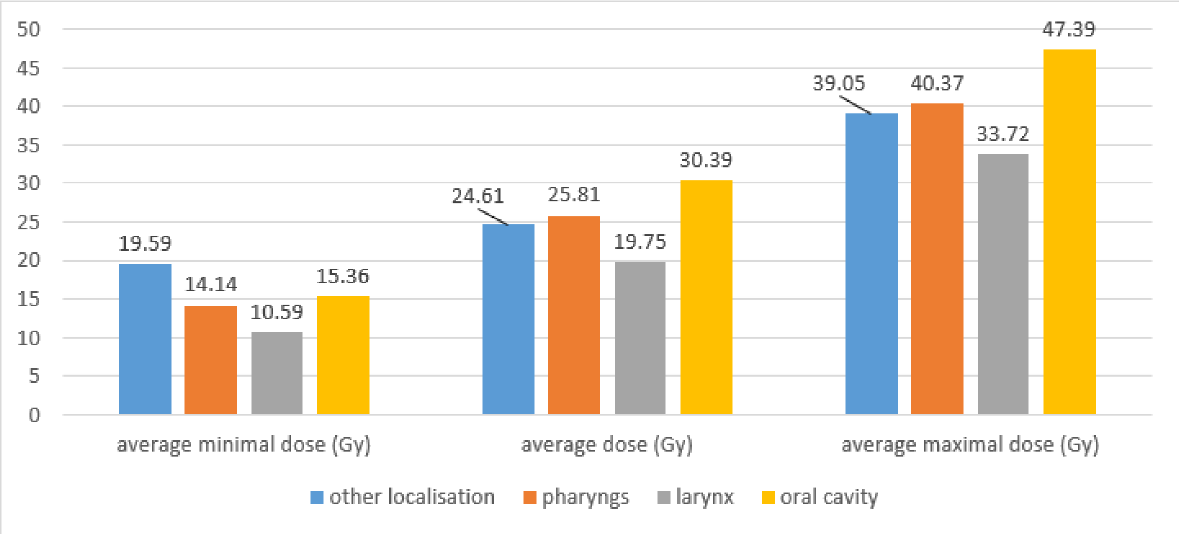

Figure 4- Deposited minimum dose, average dose and maximum dose to the lip area, taking into account the location of the cancer and the irradiation area

Furthermore, the doses received in the area of the upper and lower lip were analyzed, taking into account the therapy performed. The results in all groups for the minimum, average and maximum doses were similar, which is particularly noteworthy because in postoperative treatment lower total doses are usually used during radiation treatment. Slightly higher doses were observed in the group of patients treated surgically and then qualified for adjuvant radiochemotherapy, which may indicate a non-radical surgery and the need to administer a higher dose of radiation in combination with systemic treatment (Fig. 5)

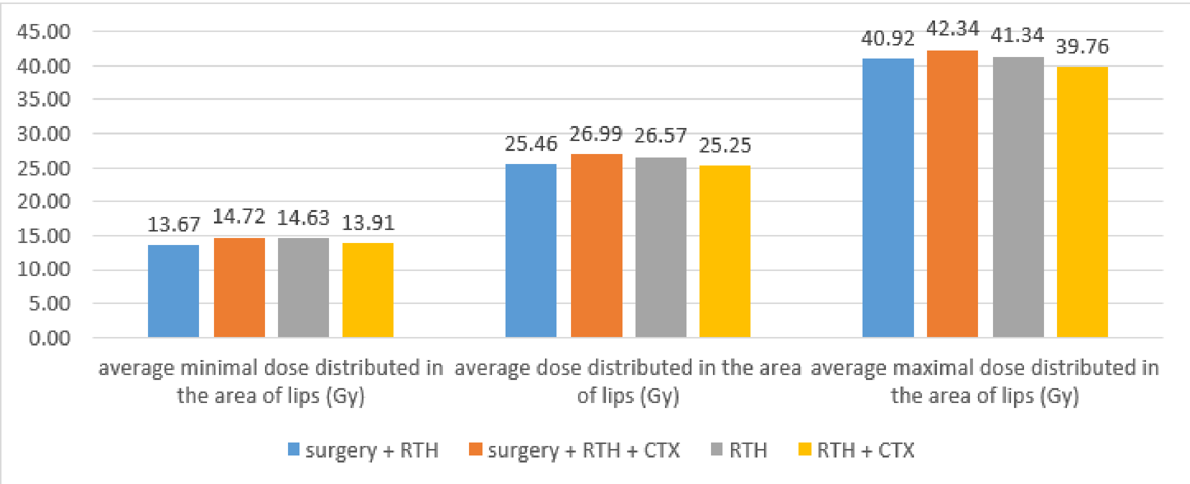

Figure 5- Analysis of the dose received on the area of the upper and lower lip, taking into account the forms of therapy

3.6 Analysis of radiation exposure results according to the Disch classification:

An important aspect of radiotherapeutic treatment is the assessment of radiation-induced reactions, most commonly utilizing the Dische scale (Tab. 3).

Table 3- Dische's acute radiation reaction scale

Weeks from the Start of Treatment	1	2	3	4	5	6	7	8
ERYTHEMA: 0-none, 1-small, 2-medium, 3-significant								
Epithelialization TYPE: 0-none, 1-small, 2-split								
SURFACE: 0-none, 1-<10%, 2-10-<50%, 3->50%								
MEMBRANE MATURATION: 0-none, 1-opalescent, 2-matte, 3-significant								
OEDEMA: 0-none, 1-small, 2-medium, 3-significant								
BLEEDING FREQUENCY: 0-none, 1-sporadic, 2-daily								
BLEEDING INTENSITY: 0-none, 1-small, 2-moderate, 3-hemorrhage								
ULCERATION CHARACTER: 0-none, 1-superficial, 2-deep								
ULCERATION SURFACE: 0-none, 1-<10%, 2; 10-<50%, 3->50%								
DYSPHAGIA: 0-no changes, 1-soft diet, 2-liquid diet, 3-enteral feeding								
PAIN FREQUENCY: 0-none, 1-intermittent, 2-continuous								
PAIN MANAGEMENT: 0-none, 1-external analgesics, 2-analgesic drugs, 3-opioids								
TOTAL:								

In the analyzed groups of the first (neck location) and second (head location) categories, we compared the minimum, mean, and maximum values of the radiation reaction grade. For all values, the radiation reaction grades were lower for the neck location, i.e., Group I, compared to Group II, which includes locations within the head region. In terms of maximum doses, there was a 4-point difference between the two groups. (Fig. 6).

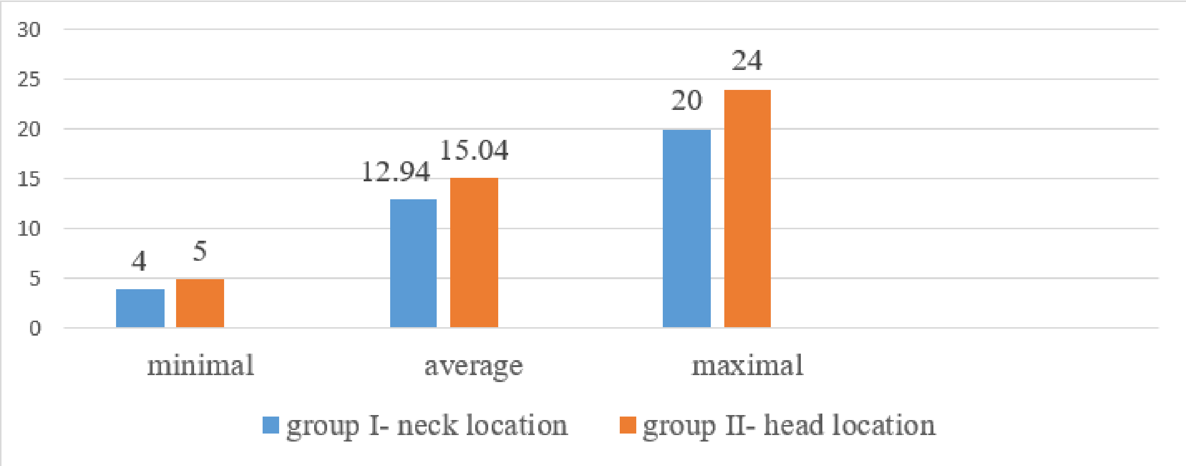

Figure 6- Radiation Reactions According to the Dische Classification, Taking into Account the Cervical Location (Group I) and Head Location (Group II)

In the subsequent stage, we analyzed the minimum, mean, and maximum radiation reaction values according to the Dische scale, taking into account the specific tumor locations. The lowest minimum radiation reaction was observed for other locations, while the highest was recorded in the group receiving radiation therapy for the pharyngeal cancer. The lowest mean radiation reaction was found for the larynx localisation, whereas the highest mean reaction was observed within the oral cavity. The maximum radiation reaction was the lowest in the group of patients with laryngeal tumors and other locations (corresponding to Group I, i.e., cervical location), whereas the highest degree of radiation reaction was noted for tumors located in the pharyngeal area (Fig. 7).

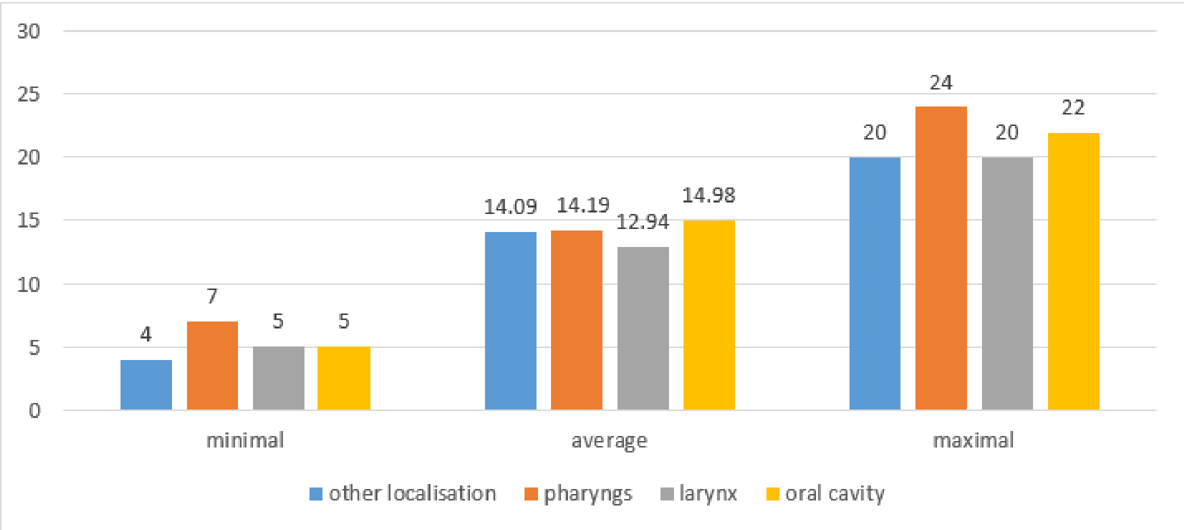

Figure 7- Radiation Reactions According to the Dische Classification with Consideration of Specific Locations

The lowest radiation reaction according to the Dische classification, based on the administered treatment, was observed in the group of patients treated with radiation therapy alone. Conversely, the highest number of side effects was noted in the radiochemotherapy group, where the minimum radiation reaction reached a level of nine. The highest average radiation reaction in this analysis was relatively similar across all groups, with a slightly lower average reaction observed in patients undergoing surgical treatment with adjuvant radiation therapy. The maximum reactions were observed in the group of patients qualified for postoperative radiochemotherapy, while results in the other groups were similar (Fig 8).

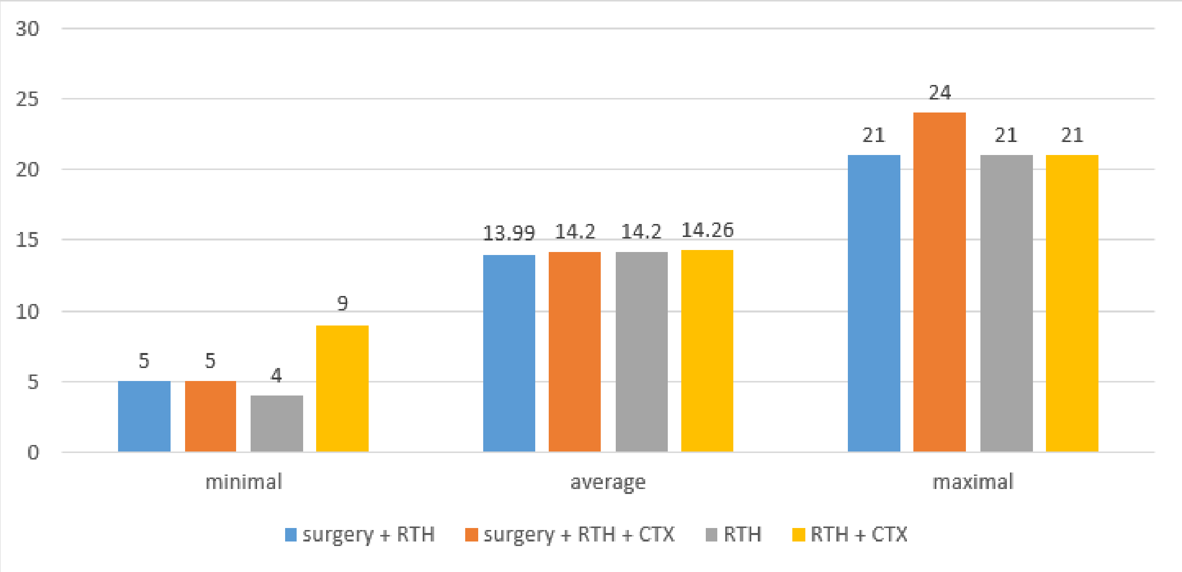

Figure 8- Mean Maximum Radiation Reaction According to the Dische Classification Based on Administered Treatment

4.7 Statistical analysis using Pearson's correlation (r) for clinical parameters:

To verify the research problem, a Pearson's correlation analysis was conducted to determine the relationship between the deposited dose to the lip and various clinical parameters, including the total dose for PTV1, PTV2 and PTV3 versus minimum, mean, and maximum doses to the lip area for both Group I and Group II, as well as differentiation based on specific locations (larynx, pharynx, oral cavity, and other locations). The relationship between the minimum, mean, and maximum doses delivered to the upper and lower lip areas, considering the treatment modality, was also assessed. Subsequently, correlations between the minimum, mean, and maximum lip doses in relation to the lowest, mean, and highest Dische classification reactions were sought.

The results of the analyses were found to be statistically insignificant ($p > 0.05$). However, it was observed that for patients with oral cavity cancer, there is a tendency for a correlation with the deposited dose to the lip, possibly due to the proximity of the therapeutic area. No correlation was observed for the laryngeal location concerning the deposited dose to the lip, indicating a significant distance between the therapeutic area and the upper and lower lips. This suggests that for this location, the lip does not need to be considered as a critical organ.

4. Results:

• Consideration should be given to treating the upper and lower lip area as a critical organ in cases of tumors primarily located within the oral cavity.

• The only location where the lip as a critical organ may be omitted is in tumors located within the larynx and in cases of patients treated surgically with additional standalone radiotherapy.

• Patients planned for intensive oncological treatment involving surgical intervention in combination with radiochemotherapy should have the upper and lower lip defined as a critical organ.

• Patients with a high Dische scale reaction in the pharyngeal area and oral cavity locations who are qualified for postoperative radiochemotherapy, should be the target group for treatment planning and implementation modifications, taking into account the upper and lower lip area as a critical organ.

5. Discussion:

Interpreting the results regarding the administered dose to the upper and lower lip area as a critical organ and its side effects in external beam radiation therapy is challenging. To date, no one has analyzed the lip area as a significant critical organ, and therefore, there is a lack of any data on this matter. The deposited average doses to the lip area varied from over 30% to nearly 50% of the prescribed dose to the high-risk area. These are high doses, indicating the need to consider contouring the lip area as a critical organ for its protection. The highest parameters of absorbed dose by the upper and lower lip area were obtained in tumors located in the oral cavity. The results obtained in this study can be interpreted based on the treatment of lip cancer using brachytherapy, where we have the most data on side effects.

In the study by Casino et al. [9], the authors observed an increase in side effects during the first 3 weeks of treatment, where progressive mucosal inflammation appeared in the treated area, which usually subsides within 1-1.5 months and rarely lasts longer than 2 months. Most patients require pharmacological treatment in the form of pain relievers and anti-inflammatory drugs. The authors reported the occurrence of unacceptable consequences (such as ulcers) if the total dose exceeded 70-75 Gy after combined treatment [9]. The most common late complications, according to the authors, are depigmentation (2.5-17%), telangiectasias (15%), and various degrees of fibrosis (8%). These side effects primarily affect cosmetic outcomes, which, although not causing functional deficits, can be challenging for the patient to accept [35]. In less than 10% of treated cases, the most significant late complication may be superficial necrosis, leading to ulceration of the lips [10].

Patients undergoing intensive treatment, i.e., those eligible for postoperative radiochemotherapy, achieve a high Dische scale reaction because they are at potentially the highest risk of early and late radiation-related complications. It should be pointed out, that higher minimal Dische's reaction in all chemiotherapy patients were observed compared to other methods, which may be an area for improvement in the future. This is a target group where contouring the lip as a critical organ should be considered. The use of more intensive treatment regimens in head and neck malignancies has led to improved treatment outcomes but has also increased its toxicity, especially with techniques like IMRT with or without chemotherapy [9,11]. During therapy, acute

radiation reactions develop, which must be closely monitored and intensively treated to ensure treatment plan adherence [1]. This is crucial because unplanned treatment interruptions and treatment prolongations are associated with worse survival and local control in patients [9,12].
Patients with severe early mucosal reactions, reflected in a high Dische scale score, experience late complications in the form of mucosal dryness and swallowing, breathing, and speech disturbances that significantly impair the quality of life. In cases of oral cavity tumors, the proximity of the lips, particularly their mobility during radiation therapy planning, necessitates additional margins, which simultaneously lead to more significant side effects for bones and soft tissues, including the upper and lower lips [13].
In Casino's study [9], patients treated for T1-T2 tongue cancer had more complications in cases with a larger treated volume. Target volumes may cause swelling and fibrosis of many normal structures in the neck region [11]. This increased rate of complications in patients requiring a larger treatment volume is also reported in other tumor locations. Mazon and colleagues [14] described 1,870 lip cancer patients treated with brachytherapy and its impact on the presence of serious functional and aesthetic consequences. The authors emphasize that the lack of available studies on large groups makes it difficult to draw definitive conclusions regarding the total dose, optimal fractional dose, and the number of fractions to achieve effective local control, survival, and good aesthetic and functional outcomes [14]. In Rocha's study, an intraoral stent was used in the treatment of lip tumors to protect surrounding healthy tissues by isolating the treatment area, thereby reducing mucosal inflammation [10]. Among the patient group in the study, no dysphagia or taste disturbances were reported, and only one patient complained of dry mouth, which occurred after 13 days of starting radiation therapy. Although the study utilized it for lip cancer protection, this method seems interesting enough to be considered for lip protection in tumors located nearby [10].
It should be emphasized that the study has several limitations that could have affected the results, including its retrospective nature, the number of patients, and the heterogeneity of the group. Nevertheless, the results suggest that lips should be considered a critical organ. Therefore, further prospective studies on a larger patient population are warranted.
On behalf of all authors, the corresponding author states that there is no conflict of interest.
All authors declare that the submitted work has not been published before (neither in English nor in any other language) and that the work is not under consideration for publication elsewhere.
The data that support the findings of this study are available from Oncology Center of prof. Franciszek Łukaszczyk in Bydgoszcz. Restrictions apply to the availability of these data, which were used under licence for this study. Data are available from the authors with the permission of Oncology Center of prof. Franciszek Łukaszczyk in Bydgoszcz
References:
1. Dutsch-Wicherek M., Bańkowska-Woźniak M., Makarewicz A. i inni., (2017) Przydatność kliniczna skali Discha w predykcji pogorszenia jakości życia i występowania zaburzeń połykania u chorych na nowotwory głowy i szyi leczonych w sposób skojarzony w Centrum Onkologii w Bydgoszczy. *Medycyna Paliatywna w Praktyce*; 11: 1-7
2. Gliński B., Ząbek M., Urbański J. (2006), Podstawowe zasady postępowania z chorymi na raka płaskonabłonkowego głowy i szyi. *Współczesna Onkologia*: 10; 263–267.
3. Wygoda A., Składowski K., Sąsiadek W. (2007), Ostry odczyn popromienny błon śluzowych u chorych na raka regionu głowy i szyi. *Współczesna Onkologia*: 11; 4, 210–219
4. Łasiński W., (1993), Anatomia głowy dla stomatologów, Wydawnictwo Lekarskie PZWL, Warszawa
5. Trotti A. (2000), Toxicity in head and neck cancer: a review of trends and issues. *Int J Radiat Oncol Biol Phys*; 47: 1-12.
6. Bentzen SM, Saunders MI, Dische S, Bond SJ. (2001), Radiotherapy-related early morbidity in head and neck cancer: quantitative clinical radiobiology as deduced from the CHART trial. *Radiother Oncol*;60: 123-135.
7. Milecki P, Szyfter K. (2003), Prognozowanie efektu napromieniania na podstawie oceny promieniowrażliwości tkanek zdrowych i guza nowotworowego – ograniczenia i możliwości. *Współczesna Onkologia*; 4:339–345
8. Ziółkowska E., Biedka M., Windorbska W., (2011), Odczyn popromienny u chorych na raka regionu głowy i szyi: mechanizmy i konsekwencje Otorynolaryngologia, 10: 147-153.
9. Casino A, (2006), Brachytherapy in lip cancer. Medicina Oral, Patología Oral y Cirugía Bucal 11:E223-229
10. Rocha B.A, (2017), Intraoral stents in preventing adverse radiotherapeutic effects in lip cancer patients, *Reports of Practical Oncology and Radiotherapy*, 450-454.
11. Guinot JL, Arribas L, Chust ML, Mengual JL, García E, Carrascosa M et al. (2003), Lip cancer treatment with high dose rate therapy. *Radiotherapy & Oncology* 69:113-115.
12. Russo G., (2008), Radiation Treatment Breaks and Ulcerative Mucositis in Head and Neck Cancer, wyd. *The Oncologist*, 886-898.
13. El Ayachy Pulsed Dose Rate Brachytherapy of Lip Carcinoma: Clinical Outcome and Quality of Life Analysis, pubmed 2021 19;13:1387.
14. Mazeron JJ, Richaud P. (1984), Lip cancer, report of 18th annual meeting of the European Curietherapy Group. *J Eur Radiother* 5:50-56.