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Clinical manifestations of I-131 induced salivary gland dysfunction in patients with thyroid carcinoma

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Aim: To carry out a retrospective analysis of the frequency and severity of clinical signs of radioiodine (^{131}I)-induced damage to the salivary glands in the early and long-term post-radiation periods, and identify risk factors for their occurrence in patients with differentiated thyroid carcinomas. **Methods:** A total of 330 patients underwent thyroidectomy with dissection of lymphatic nodes. One month after surgery, all the patients received radioiodine therapy. The dose and number of courses varied depending on the stage and morphological type of the tumor. In the late post-radiation period, the patients were surveyed with the use of a standard questionnaire, which allowed retrospective assessment of the nature and severity of symptoms of radiation-induced damage, as well as the time of their onset/subsidence. **Results:** Radiation-induced sialoadenitis of the salivary glands was observed in 51.2% of patients treated with ^{131}I. The main symptoms included pain and discomfort in the salivary glands (51.2% of patients), swelling (48.8%), transient or permanent dry mouth (38%), and distortion of taste (38%). There were statistically significant correlations between the presence and severity of the main clinical symptoms of salivary gland irradiation. A significant relationship (r = 0.91, p < 0.001) was found between swelling of the salivary glands and the feeling of pain or discomfort, which was indicative of inflammation and retention of saliva. **Conclusion:** The main factors influencing the formation of chronic radiation-induced sialoadenitis and the severity of the inflammatory process included the tumor stage, the total dose of radiopharmaceuticals, and the duration following radioiodine therapy.

Keywords: Salivary glands. Radiotherapy. Thyroid neoplasms. Sualadenitis. Xerostomia.

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Introduction

Differentiated thyroid cancers (papillary and follicular carcinomas) account for 90–95% of all thyroid tumors[1-3]. Management of such tumors requires radical surgery, including thyroidectomy with dissection of lymphatic nodes, and subsequent ablation therapy with iodine-131 (^{131}I)[4]. This approach is likely to reduce the chance of tumor recurrence and ensures a 10-year survival in more than 80% of patients[5]. Song et al.[6] reported that the effectiveness of treatment for thyroid carcinoma correlated with higher doses of radioactive iodine. However, a significant number of side effects and complications are reported in patients treated with ^{131}I. Their risk and severity, to some extent, depends on the absorbed dose of radioactive iodine. Salivary glands accumulate ^{131}I intensely, and this may lead to the complex of structural and functional impairments manifesting as acute or chronic sialoadenitis, with subsequent saliva retention, exhaustion of functional reserves, and xerostomia. Such complications, occurring in the early or late post-radiation period, require long-term treatment, the effectiveness of which is often insufficient. They are also associated with reduced quality of life.

Radiation-induced sialoadenitis is observed in 16–54% of patients undergoing radioiodine therapy[7-9]. Some studies report even higher numbers ranging from 67% to 90%[10]. Such differences are explained by the variety of clinical manifestations, the lack of clear diagnostic criteria, and the significant prevalence of sub-compensated forms in the late post-radiation period, which remain unnoticed for a long time by both patients and physicians. Jeong et al.[9] reported that between 7% and 33% of patients receiving a total ^{131}I dose of up to 300 mCi developed acute sialoadenitis in the early post-radiation period. Further, with increasing radiation doses, acute sialoadenitis occurred in more than 90% of patients[11,12]. Some authors demonstrated that the manifestations of acute radiation sialoadenitis are mostly transient and eventually resolve. However, numerous publications report the irreversible nature of salivary gland damage and the chronicity of the inflammatory process, with the formation of pathological conditions that last for years and reduce the quality of life in many patients.

Allweiss et al.[13] reported that the symptoms of chronic sialoadenitis in the late post-radiation period were seen in 11.5% of patients receiving radioiodine therapy. Alexander et al.[14] demonstrated significantly higher figures—up to 43% after a year of observation. According to Grewal et al.[15], at least 5% of patients developed severe functional deficiency and xerostomia 7 years after radioiodine therapy. Although a number of investigators state that the severity of post-radiation damage is dose-dependent, some authors consider that the immediate and long-term prognoses depend on such factors as age, somatic health, hydration, and medication, the impact of which requires additional investigation[16]. Therefore, this study aimed to carry out a retrospective analysis of the frequency and severity of clinical signs of ^{131}I-induced damage to the salivary glands in the early and long-term post-radiation periods, and identify risk factors for their occurrence in patients with differentiated thyroid carcinomas.

Methods

Patients were enrolled in the study who underwent surgical intervention for differentiated thyroid carcinoma at Komisarenko Institute of Endocrinology and Metabolism (Academy of Medical Sciences of Ukraine) between 2013 and 2019. The inclusion criteria were as follows: morphologically confirmed follicular or papillary thyroid carcinoma that underwent radical removal; at least one course of ablation therapy with ^{131}I; and more than 1 year follow-up after the initial radioiodine therapy. Exclusion criteria included age under 18 years; history of salivary gland tumor; malignancies of other sites requiring radiation or chemotherapy; low compliance and non-compliance with medical recommendations; mental disorders and CNS diseases; and patient refusal to participate in the study.

A total of 330 patients (57 men and 273 women) aged 20 to 72 (mean age 43.3 ± 9.8 years) who underwent thyroidectomy with dissection of lymphatic nodes met the abovementioned criteria. One month after surgery, all the patients received radioiodine therapy. The initial dose varied depending on the stage and morphological type of the tumor[17,18]. Those who had no diagnosed metastases or extrathyroidal extension received a therapeutic dose of 100 mCi (3700 MBq) for postoperative ablation. A dose of 150 mCi (5550 MBq) was applied in patients having regional lymph node metastases and/or tumor infiltration into the surrounding tissues. Patients with distant metastases to the lungs or bones received a dose of 200–300 mCi (7400–11100 MBq) for postoperative ablation. In most cases, the ablative effect was achieved with a single therapeutic dose.

After 4 months, diagnostic radioactive iodine scanning; neck ultrasound; and laboratory investigations, including serum thyroglobulin and antithyroglobulin antibody levels, were performed to consider the indications for additional courses of radioiodine therapy. In patients with distant metastases to the lungs (six cases), the number of ablative therapy courses was three or more.

To reduce treatment-related symptoms due to radiation damage to the salivary glands, patients were advised to increase their fluid intake and use sialogogues, such as lemon juice, chewing gum, and sugar-free candies, on the day of ^{131}I ingestion. In the late post-radiation period, patients were surveyed using a standard questionnaire designed for findings more than 1 year after initial radiotherapy, which allowed retrospective assessment of the nature and severity of symptoms of radiation-induced damage, as well as the time of their onset/subsidence. The period from the first radioiodine therapy to the survey of the studied patients ranged from 1 to 7 years (average 3 ± 3.5 years). The main questions addressed the following aspects: pain or discomfort, or swelling, in the salivary glands after radioiodine therapy, and its location and duration; dry mouth after radioiodine therapy; taste distortion; and treatment used and its efficacy. Patients were asked about the appearance of clinical symptoms or the course of the disease in the early (from a few days to 6 months) and late (more than 6 months) post-radiation periods.

The results of the study were entered into a single database. Further statistical processing was performed using the statistical package EZR v. 1.54 (graphical user interface for R statistical software version 4.0.3, R Foundation for Statistical Comput-

ing, Vienna, Austria)[19]. To identify the relationship between the studied quantitative parameters, correlation analysis was used and Spearman's rank correlation coefficients were calculated. We built logistic regression models to quantify the degree of influence of the indicated dominant factors on the clinical outcome. The significance of the logistic models was evaluated by the area under the receiver operating curve (AUC) and its 95% confidence interval (CI). Odds ratios (ORs) and 95% CIs were calculated to assess the degree of influence of the factor variables[20].

Results

The distributions of patients according to the clinical tumor stage and the total dose of radioiodine are shown in Table 1.

Table 1. Distribution of patients with respect to tumor stage and dose of ^{131}I

Total dose of radioiodine	Number of patients according to tumor stage							
	Stage I		Stage II		Stage III		Total	
	n	%	*n*	%	*n*	%	*n*	%
<3700 MBq (<100 mCi)	61	18.5	3	0.9	0	0	64	19.4
3700–5500 MBq (100–150 mCi)	144	43.6	22	6.6	41	12.5	207	62.7
>5500 MBq (>150 mCi)	37	11.2	9	2.7	13	4	59	17.9
Total	242	73.3	34	10.2	54	16.5	330	100

Among all 330 patients included in the study, 93 (28.2%) did not report any salivary gland problems in the early and late post-radiation periods. Meanwhile, 146 (44.2%) reported that clinical manifestations of radiation-induced damage occurred only in the early post-radiation period and completely resolved later, usually without any medication, and 91 (27.6%) had chronic recurrent sialoadenitis; however, the combination of clinical symptoms and their severity varied among the subjects.

Discomfort or pain after radioiodine therapy was noted by 169 patients (51.2%). Most of them (94, 28.5%) experienced this feeling only during the first days/weeks after radiation therapy, after which it resolved. These patients usually did not consult a dentist as the symptoms were short-term and resolved spontaneously. However, in 75 patients (22.7%), the condition became chronic; 46 patients (13.9%) experienced periodic discomfort and pain in the late post-surgical period, while 29 (8.8%) complained of a constant or long-term feeling of discomfort, significantly affecting their quality of life.

Major salivary gland swelling (unilateral or bilateral) was noted by 166 patients (50.2%). Of these, 92 (27.8%) experienced swelling once in the early post-radiation period, after which it resolved; 54 (16.4%) reported recurrent swelling (several times during the observation period), which resolved within a few hours or days without specific treatments; and 20 (6%) complained of recurrent and prolonged swelling. Sometimes, it did not resolve completely and was accompanied by a gradual thickening of the salivary glands.

In total, 140 patients (42.4%) had bilateral sialoadenitis and 26 patients (7.8%) had unilateral sialoadenitis. The parotid glands were affected more often than the submandibular glands (75 [22.8%] versus 50 [15.2%]).

Xerostomia (dry mouth) occurred in 125 (38%) patients. Most of these patients (63, 19.1%) experienced dry mouth symptoms in the early post-radiation period, which recurred only if they failed to keep to the recommended diet or did not drink enough. Meanwhile, 27 (8.2%) had persistent xerostomia that aggravated intermittently within the first year after radioiodine therapy, with remission intervals of varying duration, and 35 (10.7%) experienced permanent dry mouth, which affected quality of life, caused eating difficulties, and required additional hydration of the oral mucosa.

Recurrent or permanent taste alterations were reported by 125 patients (38%). They were most pronounced during the first weeks after irradiation and persisted for a long time (more than 6 months). In some patients (5%) it was permanent taste alterations. Salty, bitter, and metallic taste sensations were reported by 33 (10%), 15 (4.5%), and 43 (13.1%) patients, respectively, while 34 patients (10.4%) complained of other types of taste distortion; these were subjective and patients' descriptions varied.

Patients' histories showed that among those who complained of salivary gland problems after radioiodine therapy, 198 (60%) did not seek dental care as they had mild or no symptoms, and 109 (33%) were advised to correct their diet; use sialogogues, such as lemon juice, ascorbic acid, and pilocarpine; and massage the salivary glands in the late post-radiation period. In addition, 12 patients (3.6%) were prescribed antibacterial drugs, and 11 patients (3.4%) received non-steroidal and/or steroidal anti-inflammatory drugs. The vast majority of these patients had only a temporary improvement with no significant influence on the course of the disease.

Statistical analysis of the obtained data revealed specific relationships between individual clinical symptoms in the studied patients (Table 2).

Table 2. Correlations between ^{131}I therapy-induced salivary gland symptoms

		Pain/Discomfort	Swelling	Xerostomia	Taste alterations
Pain/Discomfort	Spearman correlation coefficient		0.917	0.374	0.389
	p		<0.0001	<0.0001	<0.0001
Swelling	Spearman correlation coefficient	0.917		0.392	0.369
	p	<0.0001		<0.0001	<0.0001
Xerostomia	Spearman correlation coefficient	0.374	0.392		0.287
	p	<0.0001	<0.0001		<0.0001
Taste alterations	Spearman correlation coefficient	0.389	0.369	0.287	
	p	<0.0001	<0.0001	<0.0001	

The most significant association was observed between the manifestations of pain and discomfort and the severity of swelling in the salivary glands. These symptoms are indicative of acute or chronic sialoadenitis and/or saliva retention. In contrast, the correlation of pain and discomfort with xerostomia was much less significant. Factors influencing the development and severity of clinical symptoms were identified using the logistic regression models. Specifically, we analyzed the relationship between the risk of chronic pain and discomfort in the salivary glands in the late post-radiation period and eight factor variables, including age, sex, number of radioiodine therapy courses, total dose of ^{131}I, duration since the first radioiodine therapy, stage of the oncologic disease, extent of tumor spread according to the TNM classification, and the presence of regional and distant metastases. The results of univariable analysis of the risk factors for development of chronic pain and discomfort are presented in Table 3.

Table 3. Coefficients of univariable logistic regression for predicting the risk of chronic pain and discomfort in the late post-radiation period

Factor variable	Model coefficient values, b±m	Significance level of the model coefficient difference from 0, *p*	Odds ratio, OR (95% CI)
Sex	0.12±0.34	0.717	–
Age	0.009±0.013	0.508	–
Number of ^{131}I therapies	-0.12±0.12	0.331	–
Total dose	0.030±0.024	0.902	–
Duration since first radioiodine therapy	-0.21±0.11	0.056	0.81 (0.66–1.01)
Tumor spread/tumor size (T)	-0.04±0.15	0.786	–
Regional metastases (N)	0.067±0.39	0.084	–
Tumor stage	0.53±0.16	<0.001	1.70 (1.24–2.32)

Univariable analysis revealed a significant increase ($p < 0.001$) in the risk of chronic pain and discomfort depending on the stage of the thyroid tumor (OR = 1.70 [95% CI 1.24–2.32] per unit of stage progression).

During the second stage of the analysis, independent risk factors associated with the development of chronic inflammation were selected for a multifactorial logistic regression model. The method of step-by-step inclusion/exclusion of risk factors (inclusion threshold $p < 0.2$ and exclusion threshold $p > 0.3$) was used to select significant risk factors. Two significant factors—time since the first radioiodine therapy and stage of the thyroid tumor—were selected. The bivariate model for predicting the risk of chronic pain or discomfort in the salivary glands in the late post-radiation period is shown in Figure 1. The AUC of the bivariate model is 0.65 (95% CI 0.60–0.70).

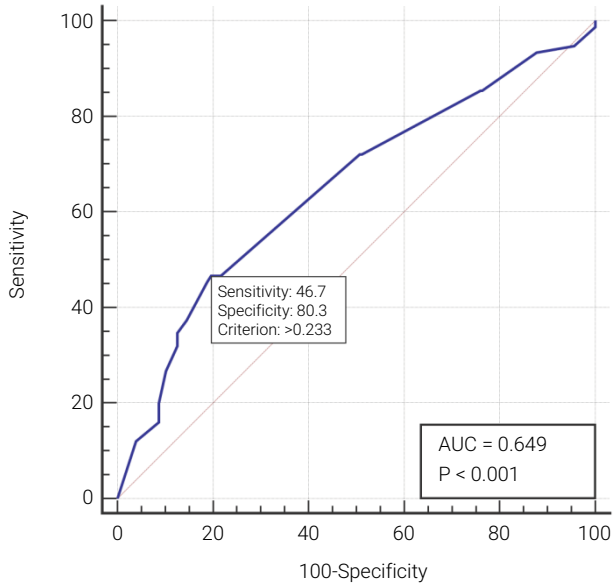

Fig.1. The receiver operating curve of the bivariate model for predicting the risk of pain and discomfort in the salivary glands in the late post-radiation period.

The bivariate model of logistic regression for predicting the risk of pain and discomfort in the late post-radiation period revealed a significant reduction (p = 0.025) in the risk of pain and discomfort in the salivary glands with time elapsed since the first radiation therapy (OR = 0.78 [95% CI 0.62–0.97] per year, with standardization by stage of the underlying disease). However, this risk was likely to rise with increasing stage of the underlying disease (OR = 1.70 [95% CI 1.24–2.32] per unit of stage progression, with standardization over time since the first radiation therapy).

While the underlying stage of the disease affected both the risk and intensity of radiation-induced sialoadenitis in patients, the total radiation dose only determined the risk of symptom onset. The total dose was significantly lower in patients who did not have any clinical manifestations of salivary gland damage (4875 ± 5047) compared with patients who had transient (6184 ± 6997) or chronic (5443 ± 2260) signs of radiation sialoadenitis.

Discussion

The problem of ^{131}I therapy-induced damage to the salivary glands has been recognized since the widespread use of radioactive iodine treatment for thyroid cancer. With the accumulation of clinical data, this problem became the subject of a large number of scientific and applied studies, which made it possible to identify the mechanisms of radiation-induced tissue, cellular, and subcellular damage to the salivary glands.

A number of authors[21,22] have considered the importance of ^{131}I as a trigger for dysfunction and chronic inflammation in the salivary glands, which may lead to complications such as loss of taste acuity, xerostomia, gastrointestinal disorders, and teeth

and periodontal injuries. A significant increase in the intensity of dental caries associated with alterations in oral microbiocenosis due to radiation-induced xerostomia was reported in patients treated with ^{131}I [23].

Recent studies revealed that iodine enters salivary gland tissue via periductal capillaries. It is then excreted, mainly by the epithelium of the intralobular striated ducts of the major salivary glands, and transported by the duct system into the oral cavity. Glycoprotein NIS (Na-I symporter) is essential for ^{131}I excretion, providing ATP-sensitive active transport of iodine ions[24]. Consequently, the concentration of radioactive iodine in the salivary glands is reported to be approximately 30–40 times higher than in blood[25]. ^{131}I-induced endothelial damage causes increased capillary permeability, and the release of plasma proteins, electrolytes, and leukocytes into the interstitial space, with raised periductal pressure. In addition, radiation-affected intralobular ducts lose their filtration capacity, and the content of serum proteins in saliva increases and salivary electrolyte composition changes dramatically[26]. Thus, the absorbed dose of ^{131}I inside the tissue causes aseptic inflammation and obstruction of the salivary ducts, and leads to decreased salivation and changes in saliva composition, and patients develop sterile inflammation due to primary and secondary salivary alteration and obstruction. As a result, patients experience dry mouth, pain and swelling in the salivary glands, and distortion of taste sensitivity. These symptoms are usually transient and resolve within a few hours or 2–3 days. However, the results of numerous clinical studies that demonstrated the nature of salivary gland dysfunction in patients undergoing ^{131}I therapy are characterized by considerable variability. Moreover, they are often contradictory[27].

According to our data, 51.2% of patients treated with radioactive iodine experienced some clinical manifestations of sialoadenitis. In the early post-radiation period, the vast majority of patients had acute radiation-induced sialoadenitis with signs of saliva retention, and in 28.5% of patients, this resolved spontaneously or with minimal therapeutic measures, such as salivary gland massage and sialogogues.

The main symptoms in the patients included in the study were associated with acute or chronic inflammation and retention of saliva. Patients complained of pain and discomfort, as well as swelling of the salivary glands. Swelling and pain occurred either within hours after application of radioactive iodine or within days or even weeks. The duration of pain and swelling varied from several hours to several days. Significant variability in the duration of remission intervals was also noted.

Chronicity of the process and the formation of more severe salivary gland disorders in the late postoperative period occurred in 75 patients (22.7%). These patients usually complained of xerostomia, and the pain became chronic, recurrent, or even permanent; swelling persisted for a long time, and thickening of the salivary glands occurred because of interstitial fibrosis. According to the literary data, the frequency of xerostomia in the late post-radiation period is variable and ranges from 2% to 43%[8,28]. In our observations, xerostomia of varying severity was seen in 38% of patients receiving radioiodine therapy; 19.1% of patients had short-term and intermittent manifestations of dry mouth, while 18.9% of patients experienced more severe and prolonged manifestations of xerostomia.

Although the signs of functional insufficiency (xerostomia) showed a significant correlation with the intensity of the inflammatory process, the value of the correlation coefficient was not high (r = 0.4, p < 0.01). Xerostomia manifestations could be very severe even with mild symptoms of acute inflammation in the early post-radiation period, and 41 patients (12.4%) who developed xerostomia did not experience pain, discomfort, or swelling.

According to Alexander et al.[14], the presence of initial symptoms of sialoadenitis (such as pain and edema) had no prognostic value for the occurrence of xerostomia. They reported that 63 of 96 patients (66%) diagnosed with radioactive iodine-induced xerostomia did not show clinical signs of sialoadenitis at an early stage. Malpani et al.[29] also failed to demonstrate any relationship between chronic salivary gland dysfunction and the severity of sialoadenitis symptoms. These dissimilarities may result from the fact that, quite often, the patient and the radiologist overlook signs of sialoadenitis in the post-radiation period, and they are not included in the statistics of complications. Patients with persistent clinical disorders do not always consult dentists; therefore, they may not receive adequate diagnosis or treatment. According to other investigators[11,12,28,30], almost 100% of patients who received ablative radioiodine therapy showed a significant decrease in both excretory and secretory functions of the large salivary glands. However, these changes can be partially compensated by the available functional reserves and preservation of the function of glands with mucous and mixed type secretions.

Our data, which are consistent with those reported by Van Nostrand[8], Alexander et al.[14], and Nakada et al.[31], confirm that the parotid salivary glands, producing predominantly serous secretion, were affected more often than the submandibular glands (1.5 times). Signs of sublingual and small salivary gland sialoadenitis in patients were virtually not observed. Interestingly, the sialoadenitis symptoms were asymmetric in 26 examined patients (7.9%). A large number of authors have studied the mechanism of asymmetric sialoadenitis of the salivary glands and the predominant sialoadenitis of serous glands[14]. Differences in radiosensitivity may result from higher concentrations of serous acinar cells in the parotid glands, which are considered more radiosensitive[32], whereas the mucous secretion of the submandibular glands may contribute to the radioprotective effect. In addition, it is believed that the relative radioresistance of the submandibular gland is due to its ability to continuously secrete without external stimulation (basal secretion)[29].

Impaired taste sensation was observed in 38% of patients included in our study. Patients described this symptom in different ways. Some of them experienced a salty taste (10%), others a bitter (4.5%) or metallic (4.5%) taste; 10.4% of patients reported a general change in taste sensitivity. The disturbances tended to be long-term and affected the quality of life. Some authors suggest that taste disturbances in patients receiving radioiodine therapy may be related to taste dysfunction (hypogeusia) due to damage to minor serous salivary glands, which are located near the lingual taste buds, also known as Ebner's glands[33,34].

Our data show that among the factors significantly influencing the occurrence of radiation-induced salivary gland manifestations, including pain and discomfort, were the stage of the thyroid tumor and the associated total dose of radiation deliv-

ered. The latter, however, affected only the occurrence, and not the intensity, of the symptoms. Another factor related to the decreased risk of the symptoms and the severity of manifestations was the duration following the onset of treatment. This confirmed Caglar et al.'s view[16] that following radiation-induced damage, the function of the salivary glands may partially restore over time and the functional deficit may be compensated by means of adaptive mechanisms. An important prerequisite for this is relevant pathogenetically targeted treatment for radiation-induced salivary gland impairments, aimed at preventing infectious complications, reducing secondary alteration, and eliminating saliva retention manifestations in patients of this category.

However, our study found that 94% of patients undergoing radioiodine therapy did not receive specialized treatment from dentists and maxillofacial surgeons in the post-radiation period. This was due to insufficient awareness of patients and radiotherapists of the current diagnostic and therapeutic options for radiation-induced sialoadenitis of the salivary glands. Patients were focused on the underlying disease and other side effects of radiation therapy, and dentists were wary of the patient's cancer history, which made it difficult to use many therapeutic techniques.

In conclusion, radiation-induced sialoadenitis of the salivary glands was observed in 51.2% of patients treated with ^{131}I. In the early post-radiation period, the patients experienced acute radiation-induced sialoadenitis, with signs of saliva retention that resolved spontaneously in 28.5% of patients without any specific medication. In 22.7% of patients, sialoadenitis was recurrent, with gradual exhaustion of functional reserves, and 18.9% of subjects developed xerostomia. Severe radiation-induced chronic sialoadenitis, which affected the ability to work and quality of life, was seen in 10.7% of patients.

The clinical picture of radiation-induced sialoadenitis of the salivary glands was variable and characterized by a combination of clinical symptoms of varying severity and duration. The main symptoms included pain and discomfort in the salivary glands (51.2% of patients), swelling (48.8%), transient or permanent dry mouth (38%), and distortion of taste (38%).

Radioiodine therapy affected the parotid glands more often than the submandibular glands (1.5 times), and 7.8% of patients exhibited asymmetric unilateral sialoadenitis, whereas 42.4% developed bilateral sialoadenitis.

The main factors influencing the formation of chronic radiation-induced sialoadenitis and the severity of the inflammatory process (pain and discomfort in the salivary glands) included the tumor stage, the total dose of radiopharmaceuticals, and the duration following radioiodine therapy. The final factor showed inverse correlation, which indicated a decrease in the activity of the inflammatory process over time. The revealed regularities indicate the necessity to prevent radiation sialadenitis in patients with thyroid tumors requiring radioiodine therapy. It should be noted that the chronicity of the process, together with the development of xerostomia, occurs in a significant percentage of cases in the absence of signs of acute post-radiation sialoadenitis in the early period. This requires long-term observation and control of salivary function in all patients undergoing radioiodine therapy courses, with special

attention to the risk group, which included patients who received radioiodine at a dose of more than 150 MBq.

Limitations of the study are mainly related to the retrospective nature of the study and the actual follow-up period of the patients included in the study group. Another limitation is the high risk of the influence of subjective factors when conducting a questionnaire. These limitations determine the expediency of providing multicenter prospective studies and comparing clinical symptoms with the results of objective functional tests, such as sialometry, sialoscintigraphy, and high-resolution MRI.

Conflict of interest

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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None.

Data Availability

Datasets related to this article will be available upon request to the corresponding author.

Author Contribution

Makarenko Viktoriia collected all patient's data, wrote the first version of the results and discussion.

Tetiana Pavlychuk performed literature review, wrote the introduction and was responsible for the study design.

Andrii Kopchak was responsible for the study design.

All authors actively participated in the manuscript's findings, revised, and approved the final version of the manuscript.

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