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Complications of radio- and radiochemotherapy in patients undergoing major salivary gland cancer surgery

Authors' Contribution:
A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
G – Funds Collection

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ABSTRACT:

Purpose: The aim of this retrospective study was to present the prevalence of early and late radiation-induced reaction and factors affecting its formation and severity in patients after adjuvant radio- or radiochemotherapy in salivary gland cancer.

Material and methods: A total of 113 patients with early and 91 with late radiation-induced reaction, irradiated in 2006–2016 were enrolled in the study. The frequency of acute mucosal radiation-induced reaction, time of onset, intensity, healing time, as well as incidence of late radiation-induced reaction from the skin and subcutaneous tissue were analysed. Factors that could influence the development and intensity of reaction were identified.

Results: Acute severity and the presence of late radiation-induced reaction do not affect overall survival. Dosage in the tumour bed site as well as the dosage in the nodal region affect the severity of acute radiation-induced mucosal reaction. The severity of early radiation-induced reaction is higher in men, more advanced patients (higher T and N+ in TNM classification), irradiated into a larger area, and those in whom two-dimensional planning and complementary chemoradiotherapy were applied. The late reaction of the skin and subcutaneous tissue was dominated by patients irradiated in the nodal regions and those with a higher intensity of early radiation-induced reaction.

Conclusions: Supplementary radiotherapy or radiochemotherapy in salivary gland cancer is associated with acceptable toxicity which has no effect on overall survival.

KEYWORDS: salivary gland tumours, radiotherapy, radiochemotherapy, radiation-induced reaction

INTRODUCTION

Salivary gland tumours comprise a histologically diverse group of cancers of the head and neck region and constitute from 3 to 11% of tumours in this region [1]. Radiotherapy or complementary chemoradiotherapy plays an important role in the treatment of this group of cancers [2]. However, it is also the cause of both early and late radiation-induced reactions; furthermore, chemotherapy used together with radiotherapy increases the toxicity of radiotherapy and causes chemotherapy-specific systemic complications [3].

Due to the complex anatomy of the head and neck region, in the irradiation area or around it there are always critical organs significant from the point of view of the patient's further functioning. These include nerve structures (brainstem, spinal cord and brachial plexus), salivary glands, oral mucosa, nasal cavity and throat, mandible, major blood vessels and muscles involved in swallowing. An arbitrary time limit between acute and late reaction is constituted by a period of 6 months from the end of irradiation, however, apart from the time criterion, the morphological image of reaction plays an important role. Acute radiation-induced reactions include radiation mucositis and dermatitis. Late radiation-induced reactions include fibrosis of the skin and mucous membranes, dry mouth (xerostomia), tissue swelling, skin discolouration, dysphagia, hearing impairment, facial paralysis, bone necrosis (osteoradionecrosis), osteoporosis and osteoporosis-related trismus [3, 4].

This paper reviews a retrospective analysis of a group of patients with major large salivary gland tumours subjected to radical surgical treatment followed by complementary radio- or radiochemotherapy. The study analysed the prevalence of both early and the most frequent late post-radiation reactions of the greatest clinical relevance. Their impact on survival was assessed, as well as the influence of various clinical and epidemiological factors and the kind of treatment performed on the type, frequency and severity of reactions.

MATERIAL AND METHODS

The initial analysis involved 126 patients with large salivary gland tumours treated with radical surgical procedure, followed by complementary radio- or radiochemotherapy in the years 2006–2016.

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The scope of surgery was dependent on the initial stage of disease on the Tumour, Node and Metastasis (TNM) staging system and consisted in the excision of tumour, salivary gland with tumour, salivary gland with selective or radical lymphadenectomy, unilateral or bilateral. All patients were found with locally advanced primary salivary gland cancer and distant metastases were excluded. All patients were qualified for complementary radio- or radiochemotherapy using the radiation methods available at the time (2D – two-dimensional technique, 3D conformal – three-dimensional technique, IMRT technique – Intensity Modulated Radiation Therapy – a technique with modulation of dosage intensity). The median total dose was 60 Gy (40-72Gy). The following schemes were used as part of chemotherapy: Cisplatin (100mg/m^2 d.1) with 5-Fluorouracil (1000mg/m^2 d.1-5) and Docetaxel (75mg/m^2 d.1) with Cisplatin (75mg/m^2 d.1) and 5-Fluorouracil (750mg/m^2 d.1-5). Among 126 patients, 113 patients were examined for at least one of the parameters of acute radiation-induced mucosal reaction (onset of reaction, time of maximum intensity, severity and healing time of reaction), all of which were determined in 98 patients. The onset of intensity of reaction, time of maximal intensity and healing time of reaction were counted in weeks from onset of radio- or radiochemotherapy, and the degree of the highest intensity was determined using RTOG criteria (Radiation Therapy Oncology Group) [5]. Data regarding the late radiation-induced reaction included the history of disease in only 91 patients, of whom 85 were also treated with acute radiation. The number of patients in particular groups is shown in Fig. 1. On the basis of documentation alone it was only possible to reliably demonstrate that a late reaction occurred without a precise indication of the time of occurrence and severity. It should only be noted that the presence of reaction indicated its occurrence in at least grade II in RTOG score [5]. The lack of reaction assessment in the remaining group of patients results from the lack of medical information regarding the reaction. Epidemiological and clinical characteristics of patients are shown in Tab. I. and II.

The first stage of statistical analysis was to show whether the radiation-induced reaction had a direct impact on survival. To this end, a group of patients with no progression of disease was distinguished. There were 84 patients who remained in this group by the end of the follow-up period. The Cox proportional-hazards model was used to analyse the influence of continuous independent variables on survival times. A correlation analysis was successively performed as regarding the dose in the postoperative site and the dose in the nodal region with the beginning, end and severity of early radiation-induced reaction and the fact of late radiation-induced reaction. Spearman's rank-order correlation was used for this purpose.

Non-parametric Mann-Whitney and Kruskal-Wallis tests were used to analyse the effect of various parameters on acute radiation-induced reaction (onset of reaction, time of maximum intensity, severity and healing time of reaction). The Mann-Whitney U test (for independent variables) was used to compare the differences between two groups of patients, and the Kruskal-Wallis test – to compare the differences between many groups of patients.

Non-parametric Mann-Whitney U test (for independent variables) was used to analyse the effect of various parameters on the occurrence of a specific type of late reaction. In order to compare the prevalence of the analysed categories depending on the type of late radiation-induced response tested, the nonparametric Chi-square test was used (for qualitative variables). The significance level in all tests was assumed as p = 0.05. The Statistica 13.1 programme was used for statistical analysis (StatSoft Polska).

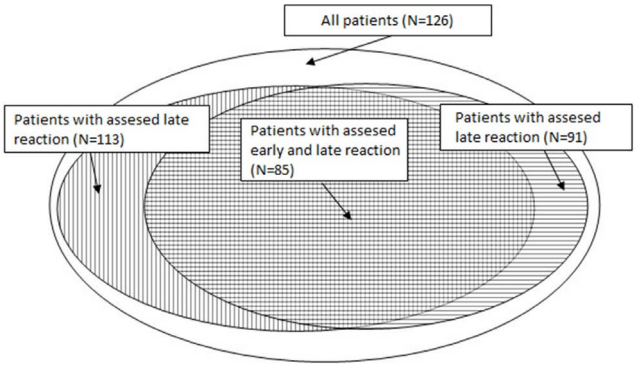

Fig. 1. Number of patients in particular groups (N – number of observations).

RESULTS

Survival analysis

Multivariate regression with Cox models, which determines the effect of the intensity of early radiation-induced reaction on survival, did not demonstrate an effect on the parameters assessed on overall survival in patients with acute radiation-induced reaction. Similarly, no effect of the number of late complications on survival was found in patients with late radiation-induced reaction. The results are shown in Tab. III.

Assessment of acute radiation-induced reaction

In Spearman's rank analysis, found was a negative correlation of the influence of dosage in the postoperative site on the onset of radiation-induced reaction and positive correlation of the dose in the postoperative site on the severity of reaction and the healing time of radiation-induced reaction (the higher the dose, the earlier the reaction; it was also more intense and took longer to heal). A positive correlation of the influence of dosage in the nodal region on the maximum severity of reaction was also demonstrated (the higher the dose, the greater the severity of reaction). The results were statistically significant (Tab. IV.).

The influence of epidemiological factors on the intensity of radiation-induced reaction was also analysed. It was found that the intensity of radiation-induced reaction was not affected by age, primary tumour localisation or level of performance according to WHO score. However, the effect of gender on both the time of reaction's occurrence, severity of reaction and healing time of reaction was demonstrated. In men, the reaction appeared earlier than in women (median in men – 2 weeks vs median in women – 3 weeks), it was more severe (median in men – grade 3 vs median in women – grade 2) and took longer to heal (median in men – 10 weeks vs median in women – 8 weeks). The influence of the stage

Tab. I. Epidemiological characteristics of patients with acute and late radiation-induced reactions.

PARAMETER	GROUP WITH ACUTE REACTION (N=113)	GROUP WITH LATE REACTION (N=91)
Age (years) – median (range)	61 (19–88)	62 (19–88)
Gender – number of patients (percent)		
– men	58(51.3%)	46 (50.5%)
– women	55(48.7%)	45 (49.5%)
WHO performance level score - number of patients (percentage)		
Level 0	45 (39.8%)	33 (36.3%)
Level 1	49 (43.4%)	46 (50.5%)
Level 2	17 (15%)	10 (11%)
Level 3	2 (1.8%)	2 (2.2%)
Primary tumour localisation - number of patients (percent)		
- parotid gland	62 (54.9%)	48 (52.7%)
- submandibular gland	51 (45.1%)	43 (47.3%)
Grade (in TNM score) - number of patients (percentage)		
I	16 (14.2%)	13 (14.3%)
II	23 (20.4%)	19 (20.9%)
III	24 (21.2%)	20 (22%)
IV	50 (44.2%)	39 (42.8%)

N – number of patients, WHO – World Health Organisation (WHO) performance level score, TNM – clinical staging according to the Tumour, Node and Metastasis classification (TNM)

of disease on the time of maximum appearance of reaction was also shown. In patients in stage I, the maximum intensity of reaction was revealed later than in patients in other stages (median in stage I – 6 weeks vs median in stages II-IV – 4 weeks). However, no statistically significant effect of the scope of surgical procedure or the length of interval between surgery and radiotherapy on the intensity of reaction was demonstrated.

In analysis of the influence of irradiation area on the severity of acute radiation-induced reaction, it was shown that in patients subject to lymph node irradiation on both sides of the neck, the maximum intensity of radiation-induced reaction occurs earlier (median 4 weeks) than in patients irradiated to other areas (median 5 weeks). Furthermore, a statistically significant difference was demonstrated between patients irradiated in different treatment planning techniques. In patients irradiated in IMRT, the reaction appeared later than in 2D and at the same time as in 3D (median 4 weeks in IMRT and 3D vs median 2 weeks in 2D), achieved the maximum later than in other techniques (median 5 weeks in IMRT vs 4 weeks in 2D and 3D) and healed faster (median 8 weeks in IMRT vs 9 weeks in 3D and 10 weeks in 2D). In the case of other parameters, the differences were not statistically significant (Tab. V.).

A statistically significant effect of the applied concurrent chemotherapy on the severity of acute radiation-induced reaction was demonstrated. The influence of chemotherapy on the remaining parameters (onset of reaction, time of maximum intensity, and healing time of reaction) was not statistically significant ($p > 0.05$).

Assessment of the occurrence of late radiation-induced reaction

Skin discolouration was more frequent in patients irradiated bilaterally (7/13, 54%) than unilaterally to the whole neck (1/11, 9%), site with regional nodes (0/5, 0%) or site alone (0/8, 0%). Also, fibrosis was more frequent in patients irradiated bilaterally (11/15, 73%) than unilaterally to the whole neck (3/14, 14%), site with regional nodes (3/6, 50%) or site alone (4/10, 40%). In turn, tissue swelling occurred more frequently in patients irradiated bilaterally (12/15, 80%) and to the site with regional nodes (6/8, 75%) than unilaterally to the entire neck (6/13, 46%) or the site alone (2/8, 25%).

It has also been shown that the time from surgery to irradiation longer or equal to 9 weeks results in lower risk of tissue oedema than the time from surgery to irradiation shorter than 9 weeks. Among patients with a longer break after surgery (≥ 9 weeks), oedema occurred in 8/21 (38%) patients, while in patients with shorter intervals after surgery (<9 weeks), oedema occurred in 18/25 (72%) patients. The results were statistically significant (Tab. VI.).

Dry mouth occurred in patients with a higher degree of acute radiation-induced response (median – grade 2, lower quartile – grade 2, upper quartile – grade 3) and did not occur in patients with a lower degree of acute radiation-induced reaction (median – grade 2, lower quartile – grade 1, upper quartile – grade 2). Xerostomia also concerned patients who experienced longer healing of acute radiation-induced disease (median – 10 weeks) and did not concern patients in whom healing of acute radiation-induced reaction lasted shorter (median – 8 weeks). In turn, oedema occurred in patients in whom acute radiation-induced reaction appeared earlier (median – 2 weeks), and did not occur in patients whose acute radiation-induced reaction appeared later (median – 3 weeks). Furthermore, skin discolouration occurred earlier in patients with acute radiation-induced reaction (median 2 weeks, lower quartile – 2 weeks, upper quartile – 3 weeks), and did not occur in patients in whom acute radiation-induced reaction appeared later (median – 2 weeks, lower quartile – 2 weeks, upper quartile – 2 weeks). Skin

Tab. II. Clinical analysis of patients with acute and late radiation.

PARAMETER	GROUP WITH ACUTE REACTION (N=113)	GROUP WITH LATE REACTION (N=91)
Time from surgery to radiotherapy - number of patients (percent)		
< 9 weeks after surgery	57 (50.4%)	48 (52.7%)
≥ 9 weeks from surgery	56 (49.6%)	43 (47.3%)
type of surgery – number of patients (percent)		
– tumour excision	17 (15%)	12 (13.3%)
– salivary gland excision	30 (26.5%)	28 (30.9%)
– tumour/salivary gland excision with selective lymphadenectomy	23 (20.4%)	19 (20.9%)
– tumour/salivary gland excision with unilateral lymphadenectomy	37 (32.7%)	26 (28.3%)
– tumour/salivary gland excision with bilateral lymphadenectomy	6 (5.4%)	6 (6.6%)
Chemotherapy paired with radiotherapy - number of patients (percent)		
– yes	19 (16.8%)	16(17.6%)
– no	94 (83.2%)	75 (82.4%)
Radiotherapy planning technique - number of patients (percent)		
– 2D	25 (22.1%)	20 (21.9%)
– 3D	26 (23%)	26 (28.6%)
– IMRT	62 (54.9%)	45 (49.5%)
Irradiation area - number of patients (percent)		
– Postoperative bed	19 (16.8%)	13 (14.8%)
– Postoperative bed with regional lymph nodes (gr. I–II or I–III)	24 (21.2%)	18 (20.4%)
– Postoperative bed with unilateral lymph nodes (gr. I–V)	45 (39.9%)	35 (39.8%)
– Postoperative bed with bilateral lymph nodes (gr. I–V)	25 (22.1%)	22 (25%)
Onset of acute reaction (weeks) – median (range)	2 (2-5)	2 (2-5)
Time of maximum severity of acute reaction (weeks) – median (range)	4 (2-7)	4 (2-7)
Maximum severity of reaction (on RTOG score) – number of patients (percent)		
0	4 (3.6%)	2 (2.4%)
I	18 (16.1%)	17 (20.2%)
II	49 (43.7%)	40 (47.6%)
III	39 (34.8%)	23 (27.4%)
IV	2 (1.8%)	2 (2.4%)
median (range)	2 (0–4)	2 (0–4)
Duration of reaction (weeks) - median (range)	10 (0–20)	8 (0–20)
Dose in postoperative site (Gy) - median (range)	60 (40–72)	60 (40–72)
Nodal area dose (Gy) – median (range)	54 (40–66)	54 (40–66)
Prevalence of late reaction – number of patients with pH/number of patients with or without reaction (percentage of patients with particular reaction in patients with or without reaction)		
– dry mouth	20/85 (23.5%)	23/86 (26.7%)
– tissue swelling	25/46 (54.4%)	26/46 (56.5%)
– tissue fibrosis	19/45 (42.2%)	21/45 (46.7%)
– skin discolouration	8/37 (21.6%)	8/37 (21.6%)
– hearing impairment	4/85 (4.7%)	5/91 (5.5%)
– other (pain in irradiated area, neck pain, otitis, taste disorders, bone marrow suppression)	9/85 (10.6%)	9/91 (9.9%)

N – number of patients, 2D – two-dimensional planning technology, – 3D- three-dimensional planning technology, IMRT – Intensity Modulated Radiation Therapy, gr. – node group, RTOG – radiation-induced reaction score according to the Radiation Therapy Oncology Group, Gy – Gray.

Tab. III. The influence of radiation-induced reaction on survival in patients with salivary gland cancer, subjected to radio-or adjuvant chemoradiotherapy after surgery.

PARAMETER	X^2	P	HR	CI 95% UPPER	CI 95% LOWER
onset of early reaction (weeks)	0.160072	0.689090	1.133272	0.613990	2.091736
time of maximum aggravation (weeks)	0.278175	0.597900	1.152195	0.680594	1.950581
maximum intensification degree (grades in RTOG score)	0.000026	0.995912	0.997677	0.409776	2.429032
Reaction healing time (weeks)	0.006118	0.937653	0.990285	0.775402	1.264718
occurrence of late reaction	0.026944	0.869615	0.955475	0.554665	1.645916

Cox multivariate analysis defining the influence of radiation-induced reaction on survival. x^2 – Chi square test value, p – materiality level, HR – Reliable risk (CI) – CI - Confidence Interval, RTOG – scale of radiation-induced reaction intensity according to the Radiation Therapy Oncology Group, Gy – Gray.

Tab. IV. Influence of radiotherapy dosage (Spearman rank analysis) on the occurrence of acute radiation-induced reaction depending on region (postoperative site, dose in the elective lymph nodes region).

ASSESSED PARAMETERS	N	R	T (N-2)	P
dose per postoperative bed and onset of reaction (Gy/weeks)	103	-0.22616	-2.3333	0.021614
dose per postoperative bed and time of maximal intensity of reaction (Gy/weeks)	113	-0.0894	-0.90653	0.366793
dose per postoperative bed and time of maximal intensity of reaction (Gy/degrees in RTOG score)	110	0.419828	4.807138	0.000005
dose per postoperative bed and reaction healing time (Gy and weeks)	97	0.385586	4.073197	0.000096
dose per postoperative bed and onset of reaction (Gy/weeks)	90	-0.122016	-1.15323	0.251938
dose per postoperative bed and time of maximum intensity of reaction (Gy/weeks)	91	-0.18353	-1.76129	0.081624
dose per postoperative bed and maximum severity of reaction (Gy/ degrees in RTOG score)	95	0.367711	3.813233	0.000247
dose per postoperative bed and reaction healing time (Gy/weeks)	82	0.187114	1.703686	0.092322

N – number of observations, R – Spearman coefficient, t – value of test with N-2 degrees of freedom, p – significance level), RTOG – intensity of radiation-induced reaction score according to the Radiation Therapy Oncology Group, Gy – Gray.

discolouration also affected the patients in whom acute radiation-induced reaction was more severe (median – grade 3) and took longer to heal (median – 14 weeks). No change of skin colour was found in patients with less severe acute radiation-induced reaction (median – grade 2) and in patients in whom acute radiation-induced reaction healed faster (median – 8 weeks). The influence of dosage on dry mouth in the nodal region was not statistically significant, but close to significance (p = 0.051) (Tab. VI.).

DISCUSSION

The analysis of retrospective results allows to conclude that standard adjuvant treatment is characterised by acceptable toxicity in both early and late radiation-induced reaction. The occurrence of reaction did not affect the most important end point, i.e. it did not cause death to a person (no complications in grade 5 in RTOG score). There was also no shortening of the survival time with severity of acute radiation-induced reaction or the occurrence of late radiation-induced reaction in patients without relapse. We did not analyse the impact of toxicity on the survival of relapsed patients, as it is difficult to distinguish the complication of treatment as a possible cause of death in patients with recurrent cancer.

Mucositis is one of the most common post-radiotherapy complications of the head and neck region. It concerns 90–100% of patients undergoing radio- or radiochemotherapy [6]. In the analysed group, acute reaction in the form of mucositis occurred in 96% of patients, of which it amounted up to 37% in grade III and IV. In the analysis of Trotti et al., grade III and IV occurred in 34% of patients with exclusive radiotherapy and 43% after radiochemotherapy [7]. Analysis of early radiation-induced reaction has shown that the higher the total dose of radiotherapy, the earlier the reaction; furthermore, it is more severe and takes longer to heal. This is particularly important in terms of high dose in the postoperative site, i.e. the region with the highest risk of relapse. There is an undoubted relationship between the risk and the severity of acute reaction, and the dose applied [8]. With the increase of the deposited dose there is damage to DNA and changes in the microenvironment caused by chemokines, pro-inflammatory cytokines and fibrous cytokines. This causes inflammation and increases radiation sensitivity. Changed intercellular interactions and the inflow of proinflammatory cells induce repair processes and, as a consequence, healing of the reaction [9]. There are many known factors responsible for the risk of occurrence and increased severity of acute radiation-induced reaction. These include factors relevant to the patient, such as age, smoking and co-morbidities. Particularly significant comorbidities include systemic connective tissue diseases, in which the inflammatory process in the skin and subcutaneous tissue and associated fibrosis worsens radiation-induced complications. Physical parameters of the treatment plan (dose, irradiation volume, irradiated area and dose heterogeneity) and the type of treatment applied (simultaneous chemotherapy, surgical treatment) also affect the intensity of treatment [9–10]. In the analysed group of patients, acute reaction was shown to be more severe in men, which may be associated with more frequent smoking in men. It is also more severe in patients with higher stages (II–IV grade in the TNM score), which is probably associated with a larger volume of irradiated tissue. Higher severity of reaction was also observed in patients irradiated to a larger area

Tab. V. The influence of individual epidemiological and clinical factors on acute radiation-induced reaction.

PARAMETER, TEST VALUE, SIGNIFICANCE LEVEL.	ONSET OF REACTION (WEEKS) Z, P	TIME OF MAXIMUM INTENSITY (WEEKS) Z, P	MAXIMUM INTENSITY OF REACTION (DEGREE IN RTOG SCORE) Z, P	HEALING TIME (WEEKS) Z, P
Age (years)	2.645, p = 0.4496	3.871, p = 0.2757	4.814, p = 0.1859	0.925, p = 0.8193
Gender (women, men)	5.125, p = 0.0236	0.101, p = 0.7508	7.003,p =0.0081	5.937, p = 0.0148
grade in WHO performance score	3.014, p = 0.3894	3.245, p = 0.3553	6.407, p =0.0934	3.058, p = 0.3827
Tumour localisation (parotid vs submandibular gland	1.941, p = 0.1635	1.399, p = 0.2368	0.478, p = 0.4892	0.027, p = 0.8692
Advancement in TNM score	1.599, p = 0.6595	13.252, p = 0.0041	3.936, p = 0.2685	2.137, p =0.5445
Time from surgery to radiotherapy (<9 weeks vs ≥ 9 weeks)	1.612, p = 0.2042	2.283, p = 0.1308	0,843, p = 0.3583	0.0431, p = 0.8354
type of surgery: tumour excision vs salivary gland excision vs tumour/salivary gland excision with selective lymphadenectomy vs tumour excision/salivary gland with unilateral lymphadenectomy vs tumour/salivary gland excision with bilateral lymphadenectomy	0.831, p = 0.9342	1.960, p = 0.7431	2.431, p = 0.6570	4.555, p = 0.3361
Chemotherapy during radiotherapy	0.385, p = 0.5350	0.750, p = 0.3865	7.063, p = 0.0079	3.825, p = 0.0505
Radiotherapy technique (2D vs 3D vs IMRT)	13.389, p = 0.0012	7.805, p = 0.0202	3.788, p = 0.1504	8.455, p = 0.0146
Radiotherapy area (site vs site with regional lymph nodes vs site with unilateral lymph nodes vs site with bilateral lymph nodes	3.095, p = 0.3772	11.827, p = 0.0080	0.904, p = 0.8244	1.446, p = 0.6949

Z – test value, p – significance level, WHO – World Health Organisation (WHO) performance level score, TNM – clinical staging according to Tumour, Node, Metastasis (TNM) score, 2D – two-dimensional planning, 3D – three-dimensional planning, IMRT – Intensity Modulated Radiation Therapy, RTOG – radiation-induced reaction intensity score according to the Radiation Therapy Oncology Group.

Tab. VI. Assessment of the influence of selected clinical-epidemiological parameters on the occurrence of late radiation-induced reaction.

PARAMETER, TEST VALUE, SIGNIFICANCE LEVEL	MUCOSAL DRYNESS (Z, P)		SWELLING (Z, P)		FIBROSIS (Z, P)		DISCOLOURATION (Z, P)		TEST
Age (years)	-0.559	0.576	-1.481	0.139	-1.638	0.101	-0.924	0.356	UMW
Gender (women, men)	0.382	0.536	0.953	0.328	0.568	0.451	0.783	0.375	X^2
grade in WHO performance score	1.354	0.716	3.900	0.272	7.491	0.057	5.355	0.147	X^2
Tumour localisation (parotid vs submandibular gland	1.890	0.169	0.540	0.462	0.102	0.750	0.109	0.740	X^2
Advancement in TNM score	2.717	0.437	2.517	0.472	1.789	0.617	3.061	0.382	X^2
Time from surgery to irradiation: <9 weeks vs ≥ 9 weeks	1.427	0.232	7.326	0.007	2.865	0.091	1.384	0.239	X^2
type of surgery: tumour excision vs salivary gland excision vs tumour/salivary gland excision with selective lymphadenectomy vs tumour excision/salivary gland with unilateral lymphadenectomy vs tumour/salivary gland excision with bilateral lymphadenectomy	1.741	0.783	1.833	0.766	0.973	0.913	3.568	0.467	X^2
Chemotherapy during radiotherapy	0.409	0.522	0.334	0.563	0.321	0.571	1.518	0.218	X^2
Radiotherapy technique (2D vs 3D vs IMRT)	2.198	0.333	1.961	0.375	2.402	0.301	2.868	0.238	X^2
Radiotherapy area (site vs site with regional lymph nodes vs site with unilateral lymph nodes vs site with bilateral lymph nodes	0.694	0.874	8.296	0.040	8.833	0.032	12.571	0.006	X^2
Onset of acute reaction (weeks)	1.650	0.099	2.950	0.003	1.260	0.208	2.347	0.019	UMW
time of maximum reaction (weeks)	1.137	0.256	1.247	0.213	0.307	0.759	1.121	0.262	UMW
Maximum degree of reaction (grades in RTOG score)	-1.975	0.048	-0.981	0.327	-1.601	0.109	-2.137	0.033	UMW
Duration of reaction (weeks)	-2.064	0.039	-0.951	0.342	-0.682	0.495	-2.550	0.011	UMW
Dose per site (Gy)	-0.150	0.881	-1.194	0.233	-0.682	0.495	-1.193	0.233	UMW
Dose per lymph nodes (Gy)	-1.952	0.051	0.073	0.942	0.761	0.447	0.142	0.887	UMW

x^2 – Chi square test, UMW – U Mann Whitney test, Z – test value, p – significance level, WHO – performance score according to the World Health Organisation (WHO), TNM – clinical staging according to the Tumour, Node, Metastasis (TNM) score, 2D – two-dimensional planning technology, 3D – three-dimensional planning technology, IMRT – Intensity Modulated Radiation Therapy, RTOG – radiation-induced reaction intensity score according to the Radiation Therapy Oncology Group, Gy – Gray.

and those who received concurrent chemotherapy. The use of 3D or IMRT reduced the severity of acute radiation-induced reaction compared to 2D, which is consistent with literature data [11].

In the analysed group of patients, late complications concerned mainly the skin, subcutaneous tissue and mucous membranes. The dominant complications were tissue swelling, xerostomia, tissue fibrosis and skin discolouration. Other complications such as hearing disorders, pain in the irradiated area, neck pain, otitis media, taste disorders or bone marrow suppression were much less common. Unfortunately, the patients' documentation regarding severity of reactions were very scarce, which undoubtedly constitutes

a limitation of the analysis. The most significant and troublesome of these complications seems to be xerostomia, which occurred in 27% in the analysed group of patients. Literature data indicate a 40% incidence of this complication [12]. The risk of dry mouth is directly related to the size of irradiated area and the dose applied [13]. The smaller the irradiated area, the greater the dose tolerated by the patient in this area. Studies indicate that the mean dose limit for the parotid gland is 26 Gy, oral mucosa (in which there are small salivary glands) – 30 Gy, and submandibular gland 39 Gy [6, 13–14]. Similarly, in the analysed group of patients, the more frequent occurrence of the above symptoms was directly related to the size of irradiated area, and to a lesser extent to the radiation dose. None of the patients treated with supplemental treatment showed osteoradionecrosis. It is a rare complication in patients with salivary gland cancer after complementary radiotherapy. In one of the studies, its occurrence was reported in 2 out of 106 irradiated patients [15]. Another complication characteristic of radiotherapy of salivary gland tumours, especially of the parotid gland, is hearing loss, which affected 6% of patients in the analysed group. Literature data indicate that sub-clinical hearing damage (up to 10dB) after radiotherapy in cancer of the parotid gland may affect 36% of patients [16]. In the analysed group of patients, there were no cases of secondary neoplasia in the irradiated area, although studies indicate that secondary cancers concern about 1% of patients and are 43% more common than in the general population [17].

In the analysed group of patients, patients with more severe acute radiation were found with more frequent late complications. The pathomechanism of this phenomenon consists in the recruitment and activation of fibroblasts with the deposition of extracellular matrix. This occurs in response to acute inflammation caused by radiation damage [18]. In response to the influx of neutrophils to the foci, there is an increased expression of intercellular adhesion molecule 1 (ICAM-1) and platelet endothelial cell adhesion molecule (PECAM-1) on the disrupted endothelial surfaces, which contributes to for extravasation of neutrophils and migration to tissues. When these cells come into contact with the fragments of collagen and fibronectin, they release pro-inflammatory cytokines, such as tumour necrosis factor-α (TNF-α), interleukin-1 (IL-1) and interleukin-6 (IL-6). This leads to a deeper inflammatory response and migration of fibroblasts to the damaged tissue. There is thickening of the tissue, fibrosis and abnormal vascularity, which in turn leads to thinning and weakening of the skin [18].

CONCLUSIONS

Supplementary radiotherapy or radiochemotherapy in salivary gland cancer is associated with acceptable toxicity which has no effect on overall survival. The prevalence of both early and late radiation-induced reaction concerns the vast majority of patients. Dosage in the tumour bed site as well as the dosage in the nodal region affect the severity of acute radiation-induced mucosal reaction. The severity of early radiation reaction is higher in men, more advanced patients (higher T and N+ in TNM score), irradiated to a larger area, and those in whom 2-D planning and complementary chemoradiotherapy have been used. The late reaction of the skin and subcutaneous tissue was dominant in patients irradiated for a larger area and in those with more severe early radiation hypersensitivity reactions.

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