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ORIGINAL RESEARCH

The Role of Prognostic Factors in Salivary Gland Tumors Treated by Surgery and Adjuvant Radio- or Chemoradiotherapy – A Single Institution Experience

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Purpose: Salivary gland neoplasms are rare cancers of the head and neck region. Radical treatment in tumors of large salivary glands is surgery. Adjuvant treatment depends on the presence of risk factors that worsen the prognosis, but the role of these factors in patients treated by surgery with radio- or radiochemotherapy still remains unclear. The aim of the study is assessment of treatment results and identification of the risk factors affecting the prognosis in patients with tumors of large salivary glands subjected to adjuvant radio- or radiochemotherapy.

Patients and Methods: The study included 126 patients with local stage large salivary gland cancer who were treated surgically with adjuvant radio- or radiochemotherapy. The study excluded inoperable patients, patients with distant metastases, patients in a poor general condition and patients with contraindications to adjuvant treatment. They were treated between 2006 and 2016 and evaluated in terms of OS (overall survival), CSS (cancer-specific survival), RFS (relapse-free survival) and LRFS (local relapse-free survival).

Results: During a 44-month follow-up, 5-OS, CSS, RFS and LRFS were 55%, 68%, 60% and 73%, respectively. Multivariate analysis showed that OS was influenced by the following parameters: WHO performance status, TNM stage (T and N parameters), radicality of surgery, histopathological type, applied method of radiotherapy planning and tumor volume. WHO performance status, T and N parameters of the TNM stage and large volume of elective area influenced CSS, and the T parameter of the TNM stage, the dose below 60Gy and tumor volume influenced RFS and LRFS. Chemoradiotherapy can be used in N-positive patients.

Conclusion: The analysis indicates that the TNM grade, histopathological type, patient's condition, radicality of the procedure, technique and dose of radiotherapy are the most important prognostic factors in these patients.

Keywords: salivary gland cancer, parotid cancer, radiotherapy, radiochemotherapy, risk factors, prognosis

Introduction

Salivary gland neoplasms are rare cancers of the head and neck region. According to SEER analysis, they constitute 8.1% of tumors in this anatomical region and 0.2% of all cancers.[1] Most cases are recorded in the sixth decade of life.[2] The incidence rate in men and women is similar – the ratio of men to women is 1.3:1.[2] These tumors develop in large salivary glands (parotid glands, submandibular

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gland, sublingual gland) and small salivary glands that are found in the mucosa of the upper gastrointestinal tract and in the upper respiratory tract. The whole population is dominated by tumors of large salivary glands, and the most common among them are parotid tumors, constituting 64–80% of salivary gland tumors. 7–11% of salivary gland tumors are tumors of the submandibular gland, and less than 1% are tumors of the sublingual gland.[3] Neoplasms of small salivary glands constitute from 9% to 23%. 25% of salivary gland neoplasms are malignant and the most common of these are mucoepidermoid carcinoma (34%), adenoid-cystic carcinoma (22%) and adenocarcinoma (18%).[4]

Radical treatment in tumors of large salivary glands is based on surgery appropriate to their stage and histopathological diagnosis.[5] Adjuvant treatment (radio- or radiochemotherapy) depends on the presence of risk factors that worsen the prognosis.[5] Currently, there are no clearly defined risk factors indicating an increased likelihood of local recurrence or distant metastases in patients undergoing adjuvant therapy, or associated indications for intensification of treatment. The following study presents an analysis of the risk factors based on a retrospective assessment of the influence of individual factors on the prognosis in a group of patients with cancer of large salivary glands undergoing adjuvant treatment – radio- or radiochemotherapy.

Materials and Methods

A retrospective analysis of a group of 126 patients with cancer of large salivary glands treated in the Center of Oncology of the Lublin Region between 2006 and 2016 was conducted. The characteristics of the patients are presented in Table 1. The study included patients with local stage cancer of large salivary glands according to the TNM (T – tumor, N – nodes, M – metastases)[6] staging system (stages I–IVb, T1–4, N0–3, M0), radically treated by surgery and adjuvant radio- or radiochemotherapy. The study excluded patients not operated on, patients with distant metastases, patients in a poor general condition (with a WHO performance status score of 4) and patients with contraindications to adjuvant radio- or radiochemotherapy. The extent of surgical treatment was dependent on the initial stage of the disease according to the TNM staging system and included tumor removal, removal of the salivary gland with the tumor, removal of the salivary gland with the tumor and

Table 1 Characteristics of the Patients

Parameter	Number of Patients (Percent)/Median (Range)
Age	61.5 (19–88 years)
- 19–49	33 (26%)
- 50–61	29 (23%)
- 62–70	31 (25%)
- 71–88	33 (26%)
Gender	
- Female	66 (52%)
- Male	60 (48%)
WHO	
- 0	53 (42%)
- 1	53 (42%)
- 2	18 (14%)
- 3	2 (2%)
Location	
- parotid gland	73 (58%)
- submandibular gland	53 (42%)
Time from surgery to radio- or radiochemotherapy	
<9 weeks	61 (48%)
≥9 weeks	65 (52%)
Clinical nerve palsy	
- yes	33 (26%)
- no	93 (74%)
Radicality	
- R0	64 (51%)
- R1	51 (48%)
- R2	11 (9%)
Nerve palsy after surgery	
- yes	37 (29%)
- no	89 (71%)
Histopathological type	
- squamous cell carcinoma	29 (23%)
- adenocarcinoma	20 (16%)
- adenoid cystic	22 (17%)
- undifferentiated carcinoma	14 (11%)
- acinic cell carcinoma	13 (10%)
- other (polymorphus adenocarcinoma, salivary duct carcinoma, mucoepidermoid carcinoma high grade, mucoepidermoid carcinoma intermediate and low grade, myoepitelial carcinoma, carcinoma ex pleomorfic adenoma	4 (3%), 8 (6%), 8 (6%), 3 (2%), 3 (2%), 2 (2%)

(*Continued*)

Table 1 (Continued).

Parameter	Number of Patients (Percent)/Median (Range)
Neuroinvasion	
- yes	41 (33%)
- no	85 (67%)
Angioinvasion	
- yes	18 (14%)
- no	108 (86%)
TNM Stage	
I	18 (14%)
II	29 (23%)
III	27 (21%)
IVab	52 (41%)
T1	22 (17%)
T2	39 (31%)
T3	30 (24%)
T4	35 (28%)
N0	83 (66%)
N 1–3	43 (34%)
Technique of radiation therapy	
- 2D	26 (21%)
- 3D	29 (23%)
- IMRT	71 (56%)
Dose	60 (40–72) Gy
<60Gy	28 (22%)
≥60Gy	98 (78%)
Chemotherapy	
- yes	19 (15%)
- no	107 (85%)
Initial level of hemoglobin	
<12.5mg/dL	10 (25%)
≥12.5mg/dL	30 (75%)
Tumor volume	54.1 cm^3 (3.7–197.7) cm^3
≤10cm^3	20 (24%)
10.1–50cm^3	28 (33%)
50.1–100cm^3	24 (29%)
>100cm^3	12 (14%)
Irradiation area	
- only surgical bed with margin	25 (20%)
- surgical bed + Ind. group I–II	27 (21%)
- surgical bed + unilateral Ind.	45 (36%)
- surgical bed + bilateral Ind	28 (22%)
Tumor bed volume (dose ≥ 60Gy)	151.5cm^3 (43.6–392.1)cm^3
≤100cm^3	16 (19%)
100.1–200cm^3	33 (31%)
200.1–300cm^3	18 (21%)
>300cm^3	17 (20%)
Elective area volume (dose ≥ 50Gy)	278 cm^3 (103.2–633.4) cm^3
≤ 150cm^3	42 (50%)
150.1–300cm^3	19 (23%)
300.1–450cm^3	12 (14%)
450.1–600cm^3	8 (10%)
>600cm^3	3 (4%)

Abbreviations: R0, radical surgery; R1, microscopic nonradical surgery, R2, macroscopic nonradical surgery; Ind, lymphadenectomy.

selective or radical unilateral or bilateral lymphadenectomy. All patients were qualified for adjuvant radio- or radiochemotherapy that was administered using irradiation methods available at the time (2-D – two-dimensional technique, 3-D three-dimensional conformal technique, IMRT – intensity-modulated radiotherapy technique). The median of the total dose was 60Gy (Gray) (40–72Gy). The minimum dose that provided local control in the treated patients was 60Gy. 29 (22%) patients did not follow the original treatment plan for various reasons. In 18 (14%) patients, treatment was discontinued due to toxicity, and 11 (9%) patients discontinued the treatment, refusing its continuation. Concomitant chemotherapy based on Cisplatin was used in 19 patients.

In the study group, the following curves were analyzed: local control (LRFS – local relapse-free survival), time to relapse (RFS – relapse-free survival), overall survival time (OS – overall survival) and cancer-specific survival (CSS). The Kaplan–Meier method was used for statistical analysis. Patient follow-up was reported to the date the patient was last seen in the hospital. The study identified and determined the impact of such epidemiological factors as age, gender, WHO performance status,[7] cancer location and the time between surgical treatment and adjuvant radio- or radiochemotherapy. The analysis also included clinical factors: nerve palsy, radicality of the surgical procedure, histopathological type, TNM stage, neuro- or angioinvasion, hemoglobin level at the start of treatment, the dose at the surgical bed and elective area, irradiation area and the applied technique of radiotherapy planning. The influence of chemotherapy on OS, CSS, RFS and LRFS was analyzed as well. In patients who were irradiated to a dose of at least 60Gy at the surgical bed and the planning was carried out using a

conformal technique (3-D or IMRT), the following volume parameters were analyzed: the tumor volume, determined on the basis of CT performed before surgery, and the volume of the surgical bed and the elective area, determined on the basis of CT for treatment planning. In order to gauge the impact of the irradiation range on prognosis, the area and volume of the surgical bed and the elective area were analyzed (as continuous variable), depending on the features T (I–IVab) and N (N-negative or N-positive) on the TNM scale.

An attempt was also made to find factors that determined the decision on concurrent adjuvant therapy and the effect of concurrent adjuvant therapy on survival in different groups. The Log-rank test was used to determine the differences in OS, CSS, RFS and LRFS between patients with the presence and absence of individual factors. The Cox proportional hazard model was used to analyze the influence of continuous independent variables on survival times. A stepwise regression of the Cox model of all the aforementioned risk factors was performed. The findings of the analysis, together with statistically significant results, are presented in the paper. Spearman's rank-order correlation test was used to assess the presence of a correlation between the stage of advancement and the irradiated area or volume. Non-parametric Kruskal–Wallis tests were used to analyze the effect of tumor volume on the type of relapse. The significance level in all tests was p=0.05. The statistical analysis was conducted using Statistica 13.1 (StatSoft Poland). The present study was approved by the Ethics Committee of the Medical University in Lublin (Lublin, Poland) (approval no. KE-0254/340/2018). Written informed consent was obtained from all participants. Participants' privacy is ensured by anonymizing the data included in the manuscript and database. The study was conducted in accordance with the Declaration of Helsinki.

Results

Over the entire follow-up period, which was 44 months on average (3–195 months), 60 patients (48%) died, 37 of whom died due to the cancer (30% of all patients). In the analyzed group of patients, 2-, 5- and 10-year overall survival was 68%, 55% and 32%, respectively, and cancer-specific survival was 82%, 68% and 42%, respectively.

During the whole period of follow-up, 43 patients (34%) were recurrent. More than half of them (29 patients – 67% of all relapses) had locoregional recurrences – 23 patients (18%) at the surgical site and 6 patients (5%) at local nodes. Pulmonary metastases were the most frequent in distant relapses (7 patients – 50% metastases). In the analyzed group of patients, 2-, 5- and 10-year relapse-free survival was 69%, 60% and 44%, respectively, whereas the local relapse-free survival was 81%, 73% and 53%, respectively.

Univariate analysis allowed to conclude that the following risk factors had a statistically significant ($p<0.05$) impact on OS: age of patients at the time of disease (older patients lived shorter), WHO performance status (shorter OS in patients in a poorer condition), tumor location (slightly better prognosis for patients with tumors in the parotid gland), initial or postoperative cranial nerve palsy (presence of paralysis worsened the survival), radicality of surgery (the worst prognosis in patients with R2 resection), histopathological type (worse prognosis in patients with squamous cell carcinoma), worse prognosis in the presence of neuroinvasion. There was a deterioration in survival with an increase in the stage (including worsening of survival with an increase in the local stage of advancement – the T feature, and invasion of lymph nodes – presence of the N-positive parameter). Worse survival was also characteristic of patients who had hemoglobin level lower than 12.5mg/dl, patients who waited for adjuvant treatment more than 9 weeks after surgery, cases where the two-dimensional technique of radiotherapy planning was used, as well as cases where the dose at the surgical site was lower than 60Gy. Larger tumor volume, larger surgical bed volume, as well as larger volume of the elective area worsened overall survival. Data on 2-, 5- and 10-year survival with p-value are provided in Table 2. Multivariate analysis based on the Cox regression model allowed to conclude that the only independent risk factors that deteriorated the survival were: a higher WHO grade, non-radical surgery, squamous cell type, higher T-grade, positive N, the dose at the surgical site and volume of tumor (Figure 1A–G.) Statistically significant parameters are given in Table 3.

In the univariate analysis, the following factors were found to have a statistically significant effect on the deterioration of CSS: worse WHO performance status, nerve palsy, neuroinvasion, higher grade on the TNM scale (including higher T and positive N), two-dimensional planning technique, dose at the surgical site lower than 60Gy, larger tumor volume and volume of elective area. Data on 2-, 5- and 10-year cancer-specific survival with p-value are provided in Table 4. The multivariate analysis based on the Cox regression model allowed to conclude that the only independent

Table 2 The Influence of the Analyzed Parameters on the 2-, 5- and 10-Year Overall Survival (OS)

Parameter	Groups	2-Year OS (%)	5-Year OS (%)	10-Year OS (%)	χ^2 Test-Value	p-value
Age	19–49 50–61 62–70 71–88	88 78 62 44	72 75 53 23	72 13 16 23	**19.646**	**0.002**
Gender	Female Male	66 70	51 58	24 38	0.864	0.387
WHO	0 1 2 3	91 63 28 0	82 50 6 0	82 17 0 0	**38.469**	**<0.001**
Location	Parotid Submandibular	75 63	67 45	39 24	**1.975**	**0.048**
Clinical Nerve palsy	Yes No	39 79	27 66	19 34	**3.797**	**<0.001**
Radicality	R0 R1 R2	75 64 45	60 56 24	33 35 12	**8.200**	**0.017**
Nerve palsy after surgery	Yes No	43 80	27 68	17 33	**4.114**	**<0.001**
Histopathological type	Squamous Adenocarcinoma Cystic adenoid carcinoma Undifferentiated Acinic Other	41 84 77 67 83 74	32 61 70 32 72 64	0 33 35 19 56 45	**13.646**	**0.018**
Neuroinvasion	Yes No	50 77	34 65	20 36	**3.248**	**0.001**
Angioinvasion	Yes No	55 70	41 57	40 31	1.150	0.250
Stage	I II III IVab	94 85 62 52	94 74 58 29	51 44 26 25	**23.219**	**<0.001**
T	1 2 3 4	96 81 61 42	96 67 53 19	51 42 24 19	**30.977**	**<0.001**
N	positive negative	48 79	28 69	16 40	**4.230**	**<0.001**
Time	<9 weeks ≥9 weeks	76 60	65 43	42 19	**2.295**	**0.022**

(*Continued*)

Table 2 (Continued).

Parameter	Groups	2-Year OS (%)	5-Year OS (%)	10-Year OS (%)	χ^2 Test-Value	p-value
Technique of RT	2D 3D IMRT	29 69 83	14 59 67	14 34 31	**4.036**	**<0.001**
Dose	<60Gy ≥60Gy	35 78	26 62	9 37	**26.350**	**<0.001**
CHT	yes no	72 68	60 54	30 30	0.880	0.929
Hemoglobin level	<12.5 mg/dL ≥12.5 mg/dL	40 83	40 72	N/A N/A	**2.253**	**0.024**
Tumor volume	≤ 10 cm^3 10.1–50 cm^3 50.1–100 cm^3 >100 cm^3	95 85 63 46	95 65 51 37	51 N/A 16 N/A	**11.725**	**0.008**
Irradiation area	Only surgical bed with margin Surgical bed + Ind. group I-II Surgical bed + unilateral Ind. Surgical bed + bilateral Ind	88 78 67 43	75 63 56 23	63 39 24 8	**15.561**	**0.001**
Tumor bed volume (dose ≥ 60Gy)	≤100 cm^3 100.1–200 cm^3 200.1–300 cm^3 >300 cm^3	94 84 76 50	94 65 63 37	50 39 0 N/A	**10.050**	**0.019**
Elective area volume (dose ≥ 50Gy)	≤150 cm^3 150.1–300 cm^3 300.1–450 cm^3 450.1–600 cm^3 >600 cm^3	90 65 65 62 67	83 46 64 33 33	43 0 N/A 0 N/A	**10.725**	**0.029**

Note: Statistically significant results in bold.
Abbreviations: p, significance level; R0, radical surgery; R1, non-radical microscopic surgery; R2, non-radical macroscopic surgery; RT, radiotherapy; CHT, chemotherapy; RT, radiotherapy; 2D, two-dimensional planning; 3D, three-dimensional planning; IMRT, planning with intensity-modulated radiation therapy

risk factors that deteriorated cancer-specific survival were: a higher WHO grade, a higher T grade, positive N feature on the TNM scale and larger volume of elective area (Figure 2). Statistically significant parameters are given in Table 3.

In addition, the univariate analysis showed that higher risk of relapse occurred in patients with a worse WHO performance status, nerve palsy, presence of neuroinvasion, higher TNM (including a higher T and positive N), larger tumor volume and when the dose at the surgical site was below 60Gy. Higher risk of local recurrence occurred in patients with worse WHO performance status, squamous histopathological type, a higher TNM stage (including a higher T-feature), a dose at the surgical site below 60Gy, and in patients irradiated using two-dimensional planning. Data on 2-, 5- and 10-year relapse-free and local relapse-free survival with p-value are provided in Tables 5 and 6. In addition, the multivariate analysis allowed to conclude that the only independent risk factors worsening the relapse-free survival and local relapse-free survival were: higher T parameter on the TNM stage scale, larger tumor volume and the dose at the surgical site lower than 60Gy (Figures 3 and 4). Statistically significant parameters are given in Table 3.

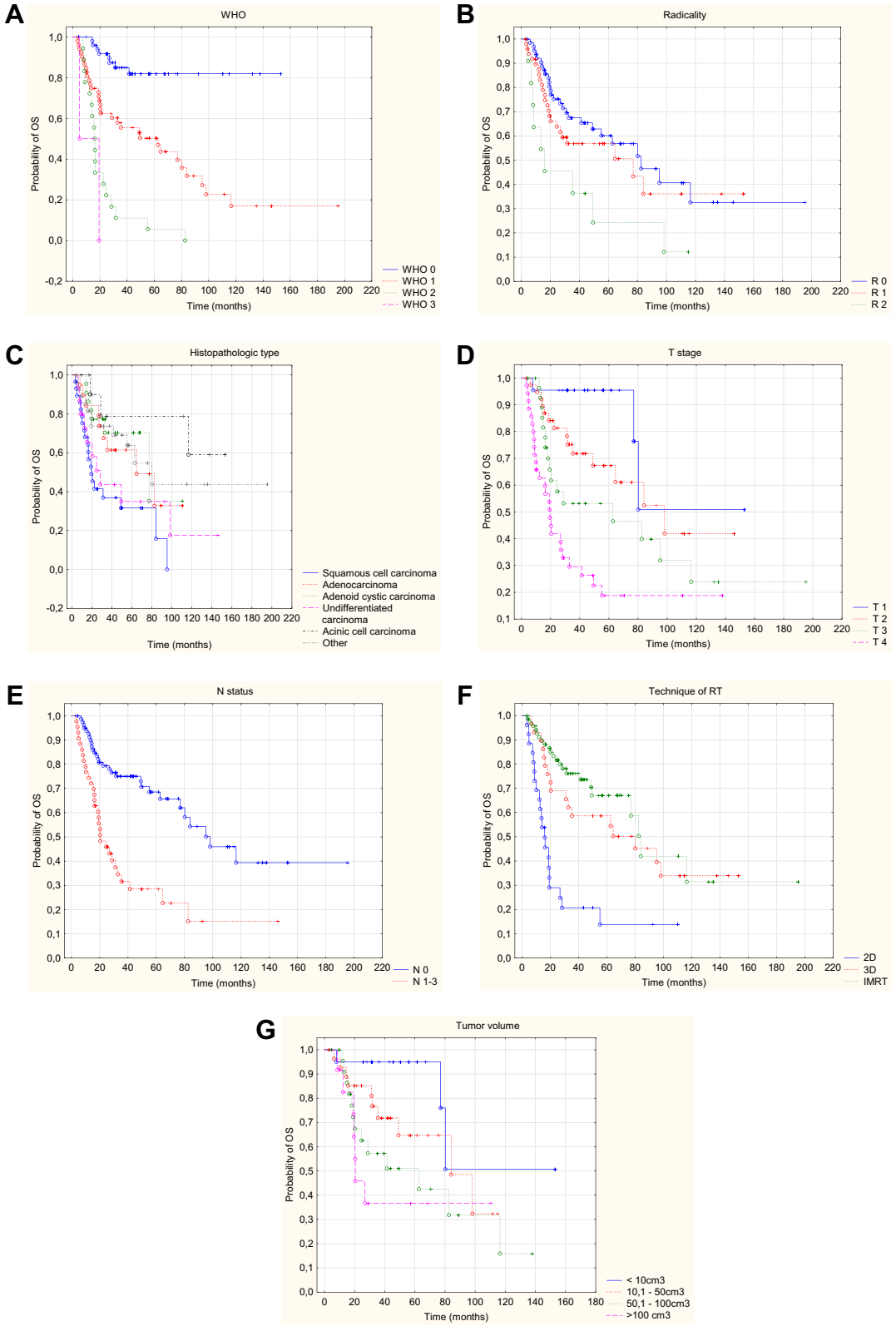

Figure 1 Kaplan–Meier curve of OS with respect to WHO status (**A**), radicalism (**B**), histopathologic type (**C**), T – stage (**D**), N – status (**E**), technique of radiotherapy (**F**), tumor volume (**G**).

Table 3 Results of Cox Multivariate Analysis

Endpoint	Parameter	Chi-square	p-value	Hazard Ratio (HR)	95% HR Lower	95% HR Upper
OS	WHO	19.540	<0.001	2.331	1.601	3.393
	Radicality	14.177	<0.001	2.020	1.401	2.914
	Squamous	7.258	0.007	2.240	1.245	4.029
	T	6.639	0.010	1.513	1.104	2.073
	N	7.097	0.007	2.131	1.221	3.719
	RT technique	5.823	0.016	0.659	0.469	0.924
	Tumor vol.	9.571	0.002	1.745	1.226	2.482
CSS	WHO	14.616	<0.001	2.341	1.514	3.620
	T	8.42013	0.004	1.779	1.206	2.626
	N	4.709	0.030	2.173	1.078	4.383
	Elective vol.	7.721	0.005	0.137	0.792	1.591
RFS	T	17.396	<0.001	2.052	1.464	2.877
	Dose	9.881	0.002	0.353	0.185	0.676
	Tumor vol.	10.326	0.001	1.978	1.305	2.999
LRFS	T	9.565	0.002	1.898	1.264	2.850
	Dose	5.436	0.019	0.391	0.177	0.861
	Tumor vol.	4.926	0.026	1.793	1.071	3.002

Abbreviations: p, significance level; CI, confidence interval; RT, radiotherapy; OS, overall survival; CSS, cancer-specific survival; RFS, relapse-free survival; LRFS, local relapse-free survival; T, tumor; N, nodes; vol, volume.

The analysis showed that the T stage on the TNM scale positively correlated with the irradiation range (R=0.254, p=0.004), the volume of the surgical bed (R=0.791, p<0.001) and the volume of the elective area (R=0.573, p<0.001). Also, the status of regional lymph nodes (features N-negative and N-positive) correlated with the irradiation range (R=0.504, p<0.001), the volume of the surgical bed (R=0.379, p<0.001) and the volume of the elective area (R=0.755, p<0.001). An analysis of the influence of the irradiation range at individual T stages on the TNM scale showed that increasing the irradiation range at stage T1 (at least for a bed with lymph nodes of groups I–III) improves CSS, and increasing the volume of the elective area (over 150 cm^3) extends RFS and LRFS. In addition, at T4, increasing the volume of the elective area (over 300 cm^3) extends LRFS (p<0.05, Table 7). In the remaining stages (T2–T3), neither the range nor the volume of irradiation affected any of the parameters tested (p>0.05, Table 7). In the case of patients with the N-negative feature, increasing the irradiation range (at least for a bed with lymph nodes of groups I–III) extended CSS and RFS. Irradiation range did not affect prognosis in patients with the N-positive feature. Also, the volume of irradiation (volume of the surgical bed, volume of the elective area) did not affect the prognosis, neither in patients without lymph node metastases (N-negative) nor in patients with lymph node metastases (N-positive) (Table 8).

The median tumor volume in the entire analyzed group was 54.1 cm^3. In the group of patients without relapse, the median volume was 48.5 cm^3, in the group of patients with local recurrence – 66.5 cm^3, and in the group of patients with generalized relapse – 68.9 cm^3. The differences were not statistically significant (Kruskal–Wallis test: H (2, N=84) = 2.629 p=0.269).

The retrospective analysis did not show any effect of chemotherapy on OS, CSS, RFS and LRFS. The results are shown in Tables 2, 4 and 5. The frequency of chemotherapy in groups of patients with selected parameters was analyzed, and then the results of treatment were compared in patients with chemoradiotherapy and patients with only radiotherapy. There were no differences in the frequency of chemotherapy in patients with a different local stage – T parameter ($\chi2$=1.492, p=0.684), radical or non-radical surgery ($\chi2$=0.030, p=0.862), with and without neuroinvasion ($\chi2$=0.390, p=0.530), and with or without angioinvasion ($\chi2$=2.640, p=0.104). However, there was a significantly more frequent use of concurrent adjuvant therapy in patients with squamous cell carcinoma ($\chi2$=4.600, p=0.032) and metastases in regional lymph nodes ($\chi2$=11.710, p<0.001). The influence of chemotherapy on OS, CSS, RFS and LRFS was analyzed in a group of patients with squamous cell

Table 4 The Influence of the Analyzed Parameters on the 2-, 5- and 10-Year Cancer-Specific Survival (CSS)

Parameter	Groups	2-Year CSS (%)	5-Year CSS (%)	10-Year CSS (%)	χ^2 Test-Value	p-value
Age	19–49 50–61 62–70 71–88	82 89 84 73	75 81 73 40	75 20 22 40	3.037	0.386
Gender	Female Male	80 84	64 73	35 52	0.956	0.339
WHO	0 1 2 3	94 80 50 0	86 68 11 0	86 27 0 0	**19.412**	**<0.001**
Location	Parotid Submandibular	83 81	62 75	36 50	1.068	0.285
Clinical nerve palsy	Yes No	61 89	47 75	38 41	**2.292**	**0.021**
Radicality	R0 R1 R2	84 79 90	69 69 72	43 43 36	1.444	0.485
Nerve palsy after surgery	Yes No	66 88	46 77	33 42	**2.740**	**0.006**
Histopathological type	Squamous Adenocarcinoma Cystic adenoid carcinoma Undifferentiated Acinic Other	64 94 82 80 100 83	55 69 74 60 87 72	0 37 37 30 65 72	6.758	0.239
Neuroinvasion	Yes No	73 86	54 75	36 45	**2.050**	**0.040**
Angioinvasion	Yes No	68 85	50 71	50 43	1.390	0.164
Stage	I II III IVab	100 92 74 74	100 79 74 43	80 48 38 37	**16.118**	**0.001**
T	1 2 3 4	100 91 76 62	100 78 66 33	80 49 34 33	**22.324**	**<0.001**
N	Positive Negative	67 89	43 79	23 51	**3.511**	**<0.001**
Time	<9 weeks ≥9 weeks	85 79	73 61	54 28	1.444	0.146

(*Continued*)

Table 4 (Continued).

Parameter	Groups	2-Year CSS (%)	5-Year CSS (%)	10-Year CSS (%)	χ^2 Test-Value	p-value
Technique of RT	2D 3D IMRT	53 81 90	25 73 76	25 50 36	**3.718**	**0.004**
Dose	<60Gy ≥60Gy	50 89	37 75	13 49	**11.013**	**<0.001**
CHT	Yes No	82 82	68 68	34 42	0.489	0.625
Hemoglobin level	<12.5 mg/dL ≥12.5 mg/dL	64 86	64 75	N/A N/A	1.016	0.310
Tumor volume	≤ 10 cm^3 10.1–50 cm^3 50.1–100 cm^3 >100 cm^3	100 92 85 64	100 73 64 51	80 N/A 24 N/A	**9.572**	**0.022**
Irradiation area	Only surgical bed with margin Surgical bed + Ind. group I–II Surgical bed + unilateral Ind. Surgical bed + bilateral Ind	91 92 86 56	77 74 78 30	66 N/A 39 10	**17.747**	**<0.001**
Tumor bed volume (dose ≥ 60Gy)	≤ 100 cm^3 100.1–200 cm^3 200.1–300 cm^3 >300 cm3	100 90 87 74	100 72 72 54	80 43 0 N/A	6.581	0.086
Elective area volume (dose ≥ 50Gy)	≤ 150 cm3 150.1–300 cm^3 300.1–450 cm^3 450.1–600 cm^3 >600 cm^3	95 82 87 83 66	87 66 87 44 33	56 0 N/A N/A N/A	**9.978**	**0.044**

Note: Statistically significant results in bold.
Abbreviations: p, significance level; R0, radical surgery; R1, non-radical microscopic surgery; R2, non-radical macroscopic surgery; RT, radiotherapy; CHT, chemotherapy; RT, radiotherapy; 2D, two-dimensional planning; 3D, three-dimensional planning; IMRT, planning with intensity-modulated radiation therapy.

carcinoma and in patients with lymph node metastases. There were no statistically significant differences between patients with squamous cell carcinoma who received chemoradiotherapy and those who received only radiotherapy in terms of OS ($\chi2$=1.279, p=0.201), CSS ($\chi2$=1.139, p=0.255), RFS ($\chi2$=1.147, p=0.251) and LRFS ($\chi2$=0.799, p=0.424). There were, however, statistically significant differences between patients with lymph node metastases and without lymph node metastases (in favor of patients with N-negative) in OS ($\chi2$=3.177, p=0.001) and in CSS ($\chi2$=2.463, p=0.014) in favor of patients with chemoradiotherapy, without statistically significant differences in RFS ($\chi2$=1.738, p=0.082) and LRFS ($\chi2$=0.457, p=0.648).

Discussion

The study indicates a relatively good prognosis in patients with local stage salivary gland cancer who have undergone surgery followed by adequate adjuvant treatment, although a relapse (local or distant) makes it significantly worse.[8] In the studied group of patients, 5-OS, 5-CSS, 5-RFS and 5-LRFS were 55%, 68%, 60% and 73%, respectively. These

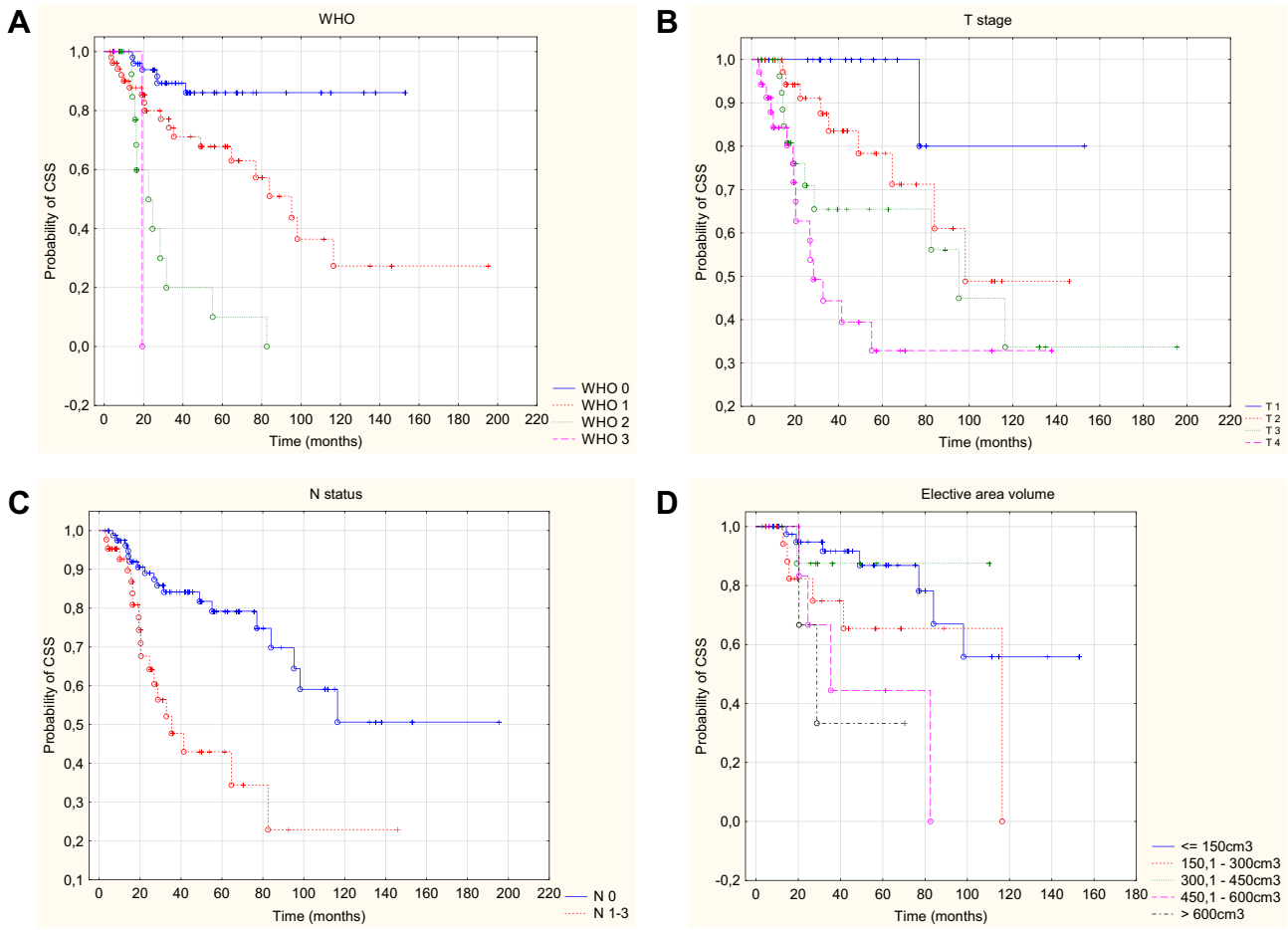

Figure 2 Kaplan–Meier curve of CSS with respect to WHO status (**A**), T – stage (**B**), N – status (**C**), elective area volume (**D**).

results are slightly lower than in the available literature. In the study by Al-Mamgani et al,[9] which involved 186 patients undergoing radiotherapy, 5-year OS, CSS, DFS and LRC were 68%, 80%, 83% and 89%, respectively. In the study by Huang et al,[10] in which 85 patients were irradiated using IMRT or 3-D methods of radiotherapy planning, 5-OS, 5-DFS and 5-LRC were 82%, 77.5% and 88.4%, respectively. In older studies, these results are slightly lower. In the study by Poorten et al,[11] 5-OS and 5-DFS were 76% and 69%, respectively, and in the study by Kirkbride et al,[12] 5-OS and 5-LRC were 68% and 81%, respectively. Only in the study by Vander Poorten et al,[13] involving 151 patients, 69% of whom underwent surgery with adjuvant radiotherapy, 5-OS and 5-DFS were worse – 46% and 64%, respectively. The reasons for these differences are complex and result from the selection of patients in each analysis. For example, in Huang et al,[10] more than half of the patients were in stage I/II on the TNM scale, and only 27% in stage IV. In the analyzed group, only 37% of patients were in stage I/II, and 41% were in stage IV. In the study by Al-Mamgani et al,[9] only 24% of patients were in stage T3–4, while in our analysis 48% of patients were in stage T3–4. In all of these studies, the prognosis in patients was significantly influenced by a variety of risk factors.

The present study discusses in detail the impact of these factors on prognosis. The Cox multivariate analysis shows that the most important risk factor for total death, cancer-specific death, total and local relapse is the stage. This is confirmed by the literature data. An extensive analysis by Spiro[14] indicates that the stage, in particular the size of the tumor over 4 cm, is a stronger prognostic factor than the histopathological type. Similarly, in the study by Renchana et al,[15] the T1–T2 tumor size is a significantly better prognostic factor than T3–4, and this factor is a more important parameter than the degree of malignancy or histopathological type. Regional nodes involvement (N-positive feature) in the study group is

Table 5 The Influence of the Analyzed Parameters on the 2-, 5- and 10-Year Relapse-Free Survival (RFS)

Parameter	Groups	2-Year RFS (%)	5-Year RFS (%)	10-Year RFS (%)	χ^2 Test-Value	p-value
Age	19–49 50–61 62–70 71–88	72 78 64 69	72 66 45 51	62 22 29 51	2.280	0.516
Gender	Female Male	69 69	53 66	45 47	1.105	0.269
WHO	0 1 2 3	88 58 43 0	85 45 21 0	75 31 0 0	**17.941**	**<0.001**
Location	Parotid Submandibular	67 73	61 60	40 50	0.789	0.430
Clinical nerve palsy	Yes No	53 75	50 64	23 52	**2.592**	**0.009**
Radicality	R0 R1 R2	70 69 68	60 45 68	45 43 34	0.669	0.715
Nerve palsy after surgery	Yes No	45 78	40 55	24 52	**2.995**	**0.003**
Histopathological type	Squamous Adenocarcinoma Cystic adenoid carcinoma Undifferentiated Acinic Other	55 64 76 64 78 83	46 64 59 64 43 73	0 43 59 43 67 73	6.525	0.258
Neuroinvasion	Yes No	55 76	50 63	27 55	**2.268**	**0.023**
Angioinvasion	Yes No	66 70	56 63	56 43	0.701	0.482
Stage	I II III IVab	100 80 70 67	88 75 65 34	88 56 39 23	**17.724**	**<0.001**
T	1 2 3 4	95 77 64 43	83 73 53 50	83 61 31 0	**20.922**	**<0.001**
N	Positive Negative	46 81	36 70	24 53	**3.117**	**0.002**
Time	<9 weeks ≥9 weeks	73 65	62 57	56 29	0.949	0.343

(*Continued*)

Table 5 (Continued).

Parameter	Groups	2-Year RFS (%)	5-Year RFS (%)	10-Year RFS (%)	χ^2 Test-Value	p-value
Technique of RT	2D 3D IMRT	44 70 76	30 70 60	30 46 45	4.928	0.085
Dose	<60Gy ≥60Gy	44 78	28 67	14 52	**3.489**	**<0.001**
CHT	Yes No	56 71	48 62	48 44	0.991	0.321
Hemoglobin level	<12.5 mg/dL ≥12.5 mg/dL	43 68	43 56	N/A N/A	1.212	0.225
Tumor volume	≤10 cm^3 10.1–50 cm^3 50.1–100 cm^3 >100 cm^3	95 76 70 44	83 71 56 44	83 N/A 0 N/A	**9.956**	**0.019**
Irradiation area	Only surgical bed with margin Surgical bed + Ind. group I-II Surgical bed + unilateral Ind. Surgical bed + bilateral Ind	83 76 74 38	68 71 70 19	55 N/A 42 19	**13.555**	**0.004**
Tumor bed volume (dose ≥ 60Gy)	≤100 cm^3 100.1–200 cm^3 200.1–300 cm^3 >300 cm^3	93 80 67 50	93 72 59 50	78 N/A N/A 0	6.204	0.102
Elective area volume (dose ≥ 50Gy)	≤ 150 cm^3 150.1–300 cm^3 300.1–450 cm^3 450.1–600 cm^3 >600 cm^3	88 70 60 58 33	85 52 N/A 58 33	56 N/A N/A 0 N/A	7.205	0.125

Note: Statistically significant results in bold.
Abbreviations: p, significance level; R0, radical surgery; R1, non-radical microscopic surgery; R2, non-radical macroscopic surgery; RT, radiotherapy; CHT, chemotherapy; RT, radiotherapy; 2D, two-dimensional planning; 3D, three-dimensional planning; IMRT, planning with intensity-modulated radiation therapy.

also a significant prognostic factor. In the multivariate Cox analysis, invasion of lymph nodes considerably deteriorated the OS, as well as the CSS and RFS in the univariate analysis. These results are confirmed by the data from the articles cited above[10,13–15.] Unfortunately, due to the number of patients (in some groups lower than 10 pt), there is a lack of statistical power to the conducted analysis stratified by the tumor T and N stage.

In the analyzed group of patients, 13 histopathological types were found, among which the most common was squamous cell carcinoma. The remaining ones included: NOS adenocarcinoma, adenoid cystic carcinoma, undifferentiated carcinoma, acinic cell carcinoma, and others, which accounted for less than 10% of all cases. The percentage of patients with individual histological types differs from their prevalence in the whole population.[16] This is due to the fact that patients with particularly prognostically bad histopathological types were qualified for radiotherapy. For instance, squamous cell carcinoma accounts for only 6–14% of salivary gland cancers in the general population.[16] It is also the type that had the statistically worst impact on overall survival. This is confirmed by the literature data. In a comprehensive analysis of over 2000 patients, Lee et al[17]

Table 6 The Influence of the Analyzed Parameters on 2-, 5- and 10-Year Local Relapse-Free Survival (LRFS)

Parameter	Groups	2-Year LRFS (%)	5-Year LRFS (%)	10-Year LRFS (%)	χ^2 Test-Value	p-value
Age	19–49 50–61 62–70 71–88	90 85 73 73	90 85 55 49	77 28 37 49	6.963	0.073
Gender	Female Male	80 82	67 79	58 55	0.870	0.384
WHO	0 1 2 3	96 74 58 0	96 63 19 0	85 43 0 0	**19.689**	**0.002**
Location	Parotid Submandibular	81 81	73 74	41 62	0.616	0.538
Clinical nerve palsy	Yes No	74 84	67 75	33 61	1.610	0.107
Radicality	R0 R1 R2	84 82 68	73 73 68	55 58 34	0.662	0.718
Nerve palsy after surgery	Yes No	83 76	74 69	58 42	1.081	0.279
Histopathological type	Squamous Adenocarcinoma Cystic adenoid carcinoma Undifferentiated Acinic Other	61 83 95 64 91 88	51 66 95 64 73 81	0 33 95 43 55 81	**11.104**	**0.049**
Neuroinvasion	Yes No	82 79	73 74	64 39	0.924	0.355
Angioinvasion	Yes No	77 82	66 74	66 52	0.756	0.449
Stage	I II III IVab	100 87 79 70	100 77 73 59	100 58 43 39	**10.256**	**0.017**
T	1 2 3 4	95 89 73 72	95 77 59 60	95 66 35 0	**12.233**	**0.007**
N	Positive Negative	69 86	61 78	40 59	1.684	0.092
Time	<9 weeks ≥9 weeks	83 79	78 66	71 34	1.247	0.213

(*Continued*)

Table 6 (Continued).

Parameter	Groups	2-Year LRFS (%)	5-Year LRFS (%)	10-Year LRFS (%)	χ^2 Test-Value	p-value
Technique of RT	2D 3D IMRT	53 89 85	35 89 74	35 59 56	**7.141**	**0.028**
Dose	<60Gy ≥60Gy	64 86	52 78	26 60	**2.653**	**0.008**
CHT	Yes No	66 84	57 76	57 54	1.202	0.229
Hemoglobin level	<12.5 mg/dL ≥12.5 mg/dL	67 75	67 59	N/A N/A	0.021	0.983
Tumor volume	≤10 cm^3 10.1–50 cm^3 50.1–100 cm^3 >100 cm^3	95 86 81 78	95 74 73 78	95 N/A 0 N/A	5.129	0.162
Irradiation area	Only surgical bed with margin Surgical bed + lnd.group I-II Surgical bed + unilateral lnd. Surgical bed + bilateral lnd	91 88 81 61	76 78 77 61	61 N/A 5 61	5.129	0.163
Tumor bed volume (dose ≥ 60Gy)	≤ 100cm^3 100.1–200 cm^3 200.1–300 cm^3 >300 cm^3	94 83 73 77	94 83 64 77	94 N/A N/A 0	5.543	0.136
Elective area volume (dose ≥ 50Gy)	≤150 cm^3 150.1–300 cm^3 300.1–450 cm^3 450.1–600 cm^3 >600 cm^3	94 80 75 58 100	88 70 N/A 58 100	63 N/A N/A 0 N/A	8.759	0.067

Note: Statistically significant results in bold.
Abbreviations: p, significance level; R0, radical surgery; R1, non-radical microscopic surgery; R2, non-radical macroscopic surgery; RT, radiotherapy; CHT, chemotherapy; RT, radiotherapy; 2D, two-dimensional planning; 3D, three-dimensional planning; IMRT, planning with intensity-modulated radiation therapy.

demonstrated that squamous cell carcinoma is worse than other histopathological types, although the difference is not statistically significant (OS: HR 0.97, CI (0.94–1.00), p=0.053). Median survival for squamous cell carcinoma, adenocarcinoma, adenoid cystic carcinoma and mucoepidermoid carcinoma was: 1.9y, 4.2y, 12.1y and 9.5y, respectively. Median time to recurrence for squamous cell carcinoma and adenoid-cystic carcinoma was 2.8y and 29.6y, respectively.[17] In the studied group of patients, those with squamous cell carcinoma had the worst prognosis, and the differences were statistically significant. 5-year OS for squamous, adenocarcinoma and adenoid-cystic carcinoma was 32%, 61% and 70%, respectively (p=0.018).

In the analyzed group of patients, the dose at the surgical site was in the range of 40–72Gy. As mentioned above, a dose lower than 60Gy was given to 29 patients. In these patients, treatment was discontinued due to its significant toxicity.[18] Patients irradiated with a dose lower than 60Gy showed worse prognosis. It had a statistically significant effect on prognosis in both the univariate analysis (for OS, CSS, RFS and LRFS) and the multivariate analysis (for RFS and LRFS). This dependence was also demonstrated by Garden et al,[19] who analyzed 198 patients with adenoid-cystic carcinoma treated by surgery with adjuvant radiotherapy. The study showed a trend towards better local control with a dose increase. This was statistically significant in patients with a positive margin with a crude control rate of

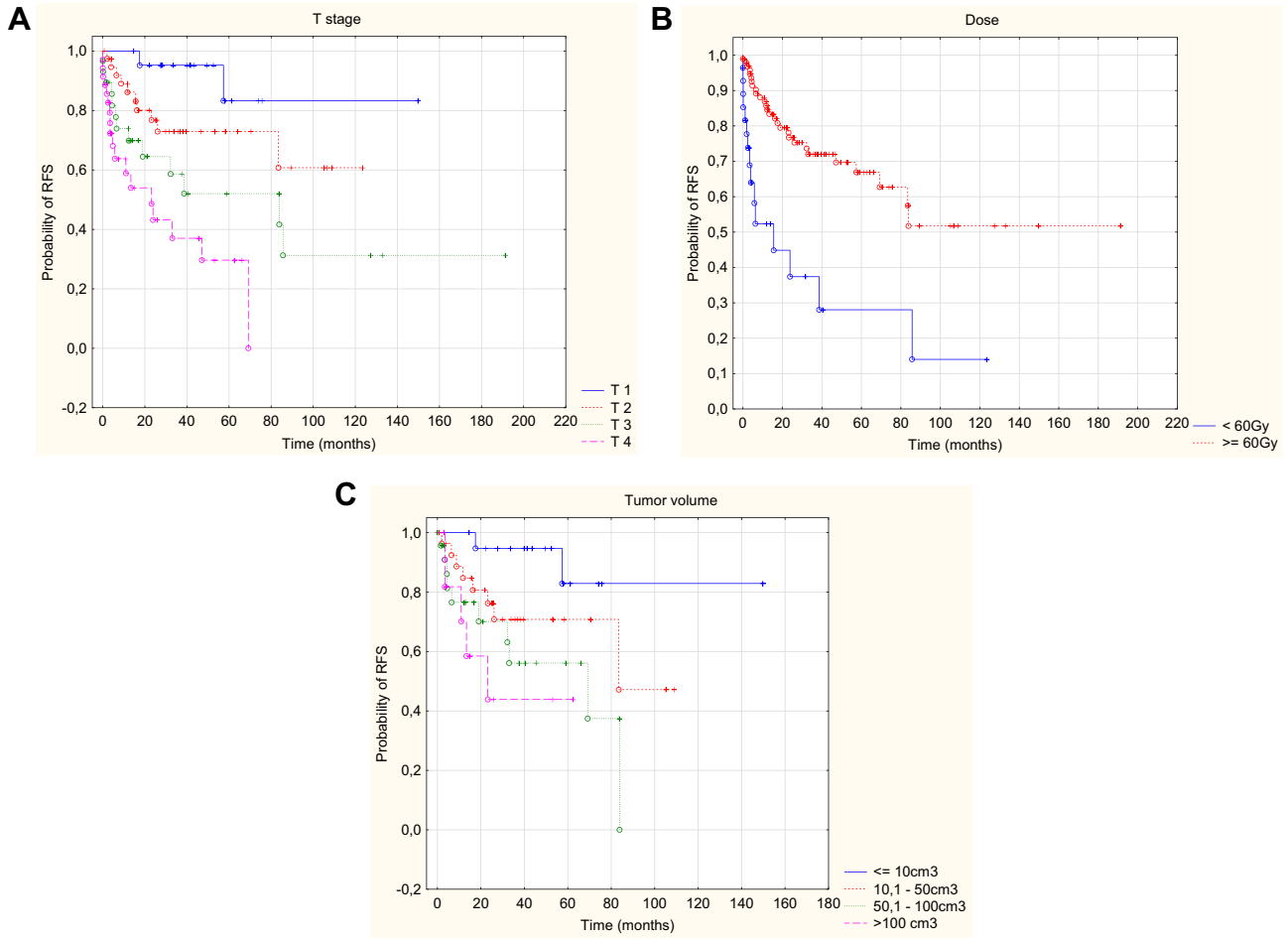

Figure 3 Kaplan–Meier curve of RFS with respect of T – stage (**A**), dose (**B**), tumor volume (**C**).

40% for doses <56Gy and 88% for doses ≥56Gy (p=0.006). Similarly, in another study by Garden et al,[20] the dose >60Gy was considered to improve local control in patients with positive margins or neuroinvasion. Also, the applied technique of radiotherapy planning influenced the results of treatment. However, due to the fact that patients were previously treated using a simpler two-dimensional planning technique, whereas in recent years they are treated with new planning techniques (3-D, then IMRT), the better treatment results may be associated with other elements of diagnostic and therapeutic procedures related to the progress in oncology. Other researchers also indicate a good prognosis in patients who have used new treatment planning techniques. In the analysis by Huang et al[10] cited above, the IMRT, 3-D and 2-D techniques were used in 77%, 23% and 0%, respectively, yielding excellent results for 5-OS and 5-DFS (82% and 77.5%, respectively), as opposed to a 17 years older study by Vander Poorten et al,[13] where 5-OS and 5-DFS were 46% and 64%, respectively.

In the examined group of patients, the following volume parameters were analyzed: tumor volume before treatment, volume of the surgical bed and nodal regions determined during radiotherapy planning. To unify the study group as much as possible, only patients treated with a dose of at least 60Gy, planned in conformal techniques, were analyzed. The impact of the volume of the tumor, surgical bed and electively irradiated lymph nodes on overall survival was demonstrated. In addition, the influence of the tumor volume on the percentage of all relapses, including local ones, was demonstrated. Similarly, many studies identify tumor volume as a determinant of prognosis.[21] In a study on larynx cancer, Knegjens et al[22] showed a significant effect of tumor volume on local control. The risk of local recurrence increases by 14% for each 10 cm^3 of tumor volume (95% CI, 8% to 21%). Also, the larger the tumor volume, the higher the risk of locoregional relapse and distant metastases. Studer et al[23] found that a 2-year nodal control was 95%, 90% and 75% for the following tumor volume ranges, respectively: 1–15 cm^3, >15–70 cm^3

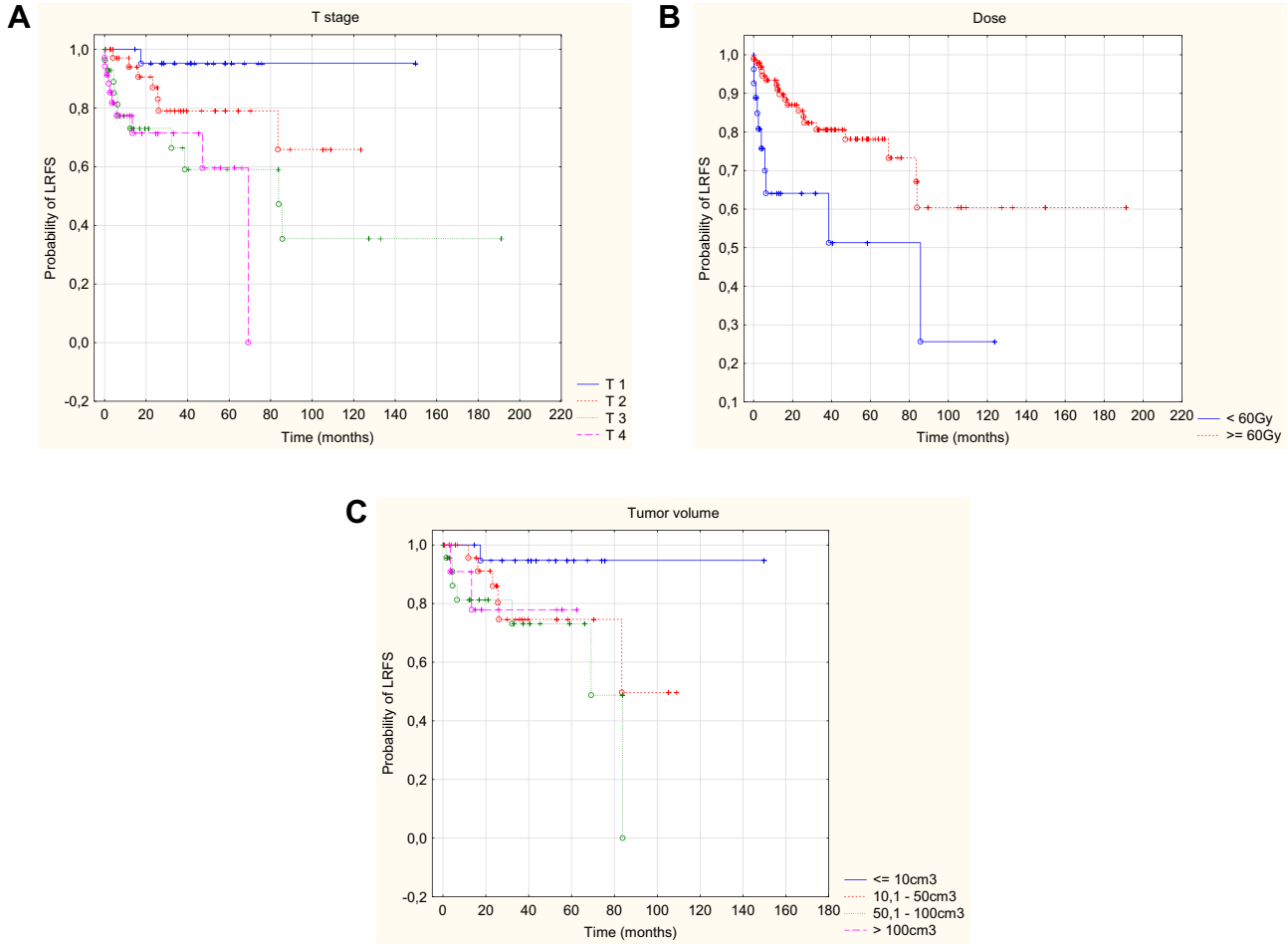

Figure 4 Kaplan–Meier curve of LRFS with respect of T – stage (**A**), dose (**B**), tumor volume (**C**).

and >70 cm^3 (p=0.04), and only 4% of patients with cancer of the head and neck region with a volume of less than 70 cm^3 had distant metastases, compared with 25% of patients with a tumor volume greater than 70 cm^3. In our study, the median tumor volume in patients without relapse was 48.5 cm^3, with local relapse – 66.5 cm^3, and with distant metastases – 68.9 cm^3. In salivary gland tumors, the adverse effect of larger tumor volume on prognosis was confirmed in a study by Almuhaimid et al.[24] The metabolic volume of MTV tumor (determined on the basis of PET-CT) was shown to be an independent factor increasing the risk of metastasis (adjusted odds ratio 4.80, 95% confidence interval 1.09–21.20; p=0.039).

The analysis of our own group of patients in various stages indicates that an increase in the irradiation range and volume of both the surgical bed and the elective area worsens the prognosis. This conclusion is misleading, given that the range and volume of irradiation positively correlate with the stage of advancement. After dividing the entire group of patients according to stages depending on the T and N features on the TNM scale, it was found that greater range and volume of irradiation not only does not worsen survival, but in some cases improves prognosis. This relationship is not as evident as in the study by Hsieh et al[25] where it was shown that, in the presence of the N-positive feature, irradiation of the area of elective lymph nodes on both sides of the neck reduces the percentage of local relapses, or as in the study by Chen et al[26] in which the use of irradiation of elective lymph nodes reduced 10-year percentage of nodal recurrences from 26% to 0%. Our analysis indicates that increasing the range of irradiation and the volume of elective areas may improve treatment results, especially at the lowest and the highest stage expressed by the T feature on the TNM scale, as well as in the absence of metastases in regional lymph nodes. Irrespective of the stage, irradiation of the surgical bed alone may increase the risk of nodal relapse. The volume of the elective lymph node area should be at least 150 cm^3 in stage T1 and at least 300 cm^3 in stage T4.

Table 7 Influence of the Irradiation Range, Surgical Bed Volume and Volume of the Elective Area in T Stages on OS, CSS, RFS and LRFS

Tumor Stage		T1		T2		T3		T4	
Test Log-Rank		**χ^2 Test-Value**	**p-value**	**χ^2 Test-Value**	**p-value**	**χ^2 Test-Value**	**p-value**	**χ^2 Test-Value**	**p-value**
Irradiation area vs:	OS	−4.432	0.218	−1.082	0.781	−6.177	0.103	−3.043	0.385
	CSS	**−9.2**	**0.026**	−3.604	0.307	−5.831	0.12	−3.647	0.302
	RFS	−5.373	0.146	−1.918	0.589	−5.479	0.14	−3.102	0.376
	LRFS	−4.697	0.195	−3.306	0.307	−2.444	0.485	−0.361	0.948
Tumor bed volume vs:	OS	0.423	0.672	−0.436	0.803	−0.984	0.611	−0.992	0.609
	CSS	0	1	−1.219	0.543	−0.448	0.799	−0.073	0.963
	RFS	0.671	0.501	−1.154	0.561	−0.48	0.786	−0.258	0.878
	LRFS	0.461	0.644	−4.453	0.107	−1.304	0.52	−1.428	0.489
Elective area volume vs:	OS	0.338	0.734	−5.265	0.071	−5.032	0.284	−0.603	0.962
	CSS	0	1	−1.249	0.535	−1.582	0.52	−2.668	0.615
	RFS	**−2.12**	**0.033**	−2.157	0.339	−0.218	0.994	−3.866	0.962
	LRFS	**−2.287**	**0.022**	−2.987	0.224	−0.397	0.982	**−11.434**	**0.022**

Note: Statistically significant results in bold.
Abbreviations: p, significance level; χ^2, chi square test; OS, overall survival; CSS, cancer-specific survival; RFS, relapse-free survival; LRFS, local relapse-free survival; T, tumor.

Table 8 Influence of the Irradiation Range, Surgical Bed Volume and Volume of the Elective Area in N Stages on OS, CSS, RFS and LRFS

Nodal Status		N0		N 1–3	
Test Log-Rank		**χ^2 Test-Value**	**p-value**	**χ^2 Test-Value**	**p-value**
Irradiation area vs:	OS	−4.409	0.22	−5.023	0.17
	CSS	**−8.608**	**0.035**	−6.808	0.078
	RFS	**−8.979**	**0.029**	−4.263	0.234
	LRFS	−6.811	0.078	−0.246	0.969
Tumor bed volume vs:	OS	−2.474	0.480	−2.896	0.408
	CSS	−3.983	0.263	−1.280	0.734
	RFS	−5.517	0.138	−1.091	0.779
	LRFS	−6.298	0.098	−2.521	0.472
Elective area volume vs:	OS	−3.766	0.152	−0.194	0.979
	CSS	−2.247	0.325	−0.716	0.870
	RFS	−2.464	0.292	−0.600	0.897
	LRFS	−3.831	0.147	−3.348	0.341

Note: Statistically significant results in bold.
Abbreviations: p, significance level; χ2, chi square test; OS, overall survival; CSS, cancer-specific survival; RFS, relapse-free survival; LRFS, local relapse-free survival; N, nodes.

In the analyzed group of patients, a deteriorating factor for OS, CSS as well as for RFS and LRFS is neuroinvasion. This is also confirmed by other studies.[27] In the study by Garden et al[19] cited above, neuroinvasion was found to be one of the risk factors that deteriorated crude failure rates from 18% to 9% (p=0.02), and in the analysis by Huang et al it affected OS (p=0.03), DFS (p=0.009) and LRC (p=0.049).

Numerous publications identify hemoglobin levels as an important determinant of prognosis.[21,28–31] Correlation of lower hemoglobin level with a worse effect of radiotherapy was demonstrated in cancers of the head and neck region, lungs, cervix and bladder.[28] In the case of head and neck cancers, the study was based primarily on the most common squamous cell carcinomas, in particular larynx cancer.[29–31] The cut-off value was considered to be 12mg/dl, below which the prognosis was worse. Studies in the available literature did not analyze the effect of hemoglobin on head and neck tumors other than squamous cell carcinomas. In the

analyzed group of patients with salivary gland cancers, the effect of hemoglobin level lower than 12.5 mg/dl on overall survival was demonstrated. The effect of low hemoglobin on the relapse rate has not been shown, which may, however, be related to the small number of patients analyzed.

A number of studies identify the radicality of the surgical procedure as a factor affecting the prognosis.[27,32–34] In our study, the radicality had a significant impact only on overall survival, both in the univariate analysis and in the multivariate analysis. Also, the age of patients at the time of the disease had a negative influence on the prognosis, which is confirmed by some other publications.[10] In addition, the WHO performance status determines the prognosis, affecting all endpoints analyzed in the study (in the multivariate analysis, only OS and CSS). Although there are no studies on this topic, the impact of the general condition seems to be indisputable and should play an important role in qualifying patients for treatment.

Our study did not show any benefits of using chemotherapy in any of the endpoints examined. This may be due to the selection of patients in particular groups. Patients who were assumed to have a worse prognosis underwent more aggressive treatment – chemoradiotherapy, so they cannot be easily compared with better prognosis patients treated with adjuvant radiotherapy. For this reason, two subgroups were analyzed, in which the number of patients undergoing chemoradiation was significantly different from the other patients in study. They were patients with squamous cell carcinoma and metastases to regional lymph nodes. A statistically significant positive effect of the use of chemotherapy on overall survival and cancer-specific survival was demonstrated only in the group with nodal metastases. There was no statistically significant effect on RFS and LRFS. There is no literature in the field of randomized trials comparing adjuvant radiochemotherapy and radiotherapy. In many cases, the addition of chemotherapy results from the extrapolation of research into other cancers of the head and neck region.[35] This is particularly evident in patients with squamous cell carcinoma.[36] Studies comparing the results of treatment of patients with chemotherapy and without chemotherapy did not show any benefits of chemotherapy,[37–42] however, these are retrospective studies on a small group of patients, and the lack of differences may result from the selection of patients mentioned earlier. Only a prospective randomized trial could show any obvious benefits of using adjuvant chemoradiotherapy.

Conclusion

The severity of the disease on the TNM scale, and in particular the T parameter, is the most important independent factor that worsens the prognosis in all the analyzed endpoints. The invasion of lymph nodes also plays a significant role in prognosis, although to a lesser extent. Among the analyzed histopathological types, the most unfavorable prognosis is in the case of squamous cell carcinoma, the presence of which is an independent factor that deteriorates the overall survival. A non-radical surgery, neuroinvasion, low hemoglobin level, high volume of tumor and a poor general condition also deteriorate survival. It is recommended to use a dose over 60Gy at the surgical bed, take into account the area of elective lymph nodes, and implement new planning techniques to reduce the risk of relapse. Although the role of adjuvant chemoradiotherapy is still unclear, it may be beneficial to patients with regional lymph node metastases. It is necessary to identify risk factors whose presence should influence the modification of adjuvant therapy in this group of patients.

Disclosure

The authors declare that there are no conflicts of interest regarding the publication of this article.

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