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COMPARATIVE ANALYSIS OF THE EFFICACY OF DEFINITIVE CHEMORADIATION THERAPY AND SURGERY FOLLOWED BY ADJUVANT RADIATION THERAPY IN ADVANCED-STAGE ORAL TONGUE CANCER

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The *aim* of the study was to compare the efficacy of definitive chemoradiation therapy (CRT) and primary surgery followed by adjuvant radiotherapy (RT) or CRT in the management of patients with stage III–IVA–B resectable oral tongue squamous cell carcinoma (OTSCC). *Materials and Methods*: It is a retrospective analysis of the treatment outcomes of 211 patients with stage III–IVA–B resectable OTSCC. The patients were divided into two groups depending on the treatment modality: 114 patients received surgery followed by adjuvant RT or CRT (S-RT/CRT) group; the definitive CRT group consisted of 97 patients. *Results:* The five-year overall survival (OS) was 57.0% in S-RT/CRT group *vs* 20.4% in CRT group; the five-year disease-free survival (DFS) in S-RT/CRT group was 56.5% *vs* 15.5%, in the CRT group. Comparison of survival curves revealed statistically significant higher OS and DFS rates in patients of S-RT/CRT group as compared with those in CRT patients (hazard ratio = 0.33 (95% confidence interval 0.23–0.47), $p < 0.001$ *vs* hazard ratio = 0.25 (95% confidence interval 0.17–0.37), $p < 0.001$). A multivariate analysis showed a statistically significant prognostic effect of the primary tumor extension cT4 ($p = 0.004$), cervical lymph node involvement cN2 ($p < 0.001$), cN3 ($p = 0.04$) and treatment modality ($p < 0.001$) on OS. There was also found a statistically significant prognostic effect of the primary tumor extension cT4 ($p = 0.02$), cervical lymph node involvement cN2 ($p < 0.001$) and treatment modality ($p < 0.001$) on DFS. 18 (15.8%) patients of S-RT/CRT group and 13 (13.4%) patients ($p = 0.77$) of CRT group developed mandibular osteoradionecrosis. *Conclusion:* Primary surgery with adjuvant RT or CRT in advanced-stage resectable OTSCC significantly increases five-year OS and DFS rates as compared to those after definitive CRT.
***Key Words*: oral tongue squamous cell carcinoma, radiotherapy, chemoradiotherapy, surgical treatment.**

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About 2,200 oral squamous cell carcinomas (OSCC) are registered annually in Ukraine, of which more than 50% are stages III–IV. The oral tongue squamous cell carcinoma (OTSCC) is diagnosed most frequently; it accounts for 45–48% of all malignancies of the oral cavity [1]. In recent decades, a number of studies have shown that definitive chemoradiation therapy (CRT) as an organ-preserving approach is an acceptable alternative to surgery followed by radiotherapy (RT) or surgery with concurrent CRT, which has been proved by similar survival rates of patients with locally advanced laryngeal and hypopharyngeal squamous cell carcinomas. Salvage surgery is considered after failed definitive CRT or the disease recurrence [2, 3]. Similar results were obtained in the treatment of locally advanced oropharyngeal cancer [4].

The role of definitive CRT as an organ-preserving approach in the management of patients with advanced-stage resectable OSCC is still unclear. Primary surgery followed by RT or CRT remains the standard in the management of patients with advanced oral cancer [5]. To our knowledge, there are no randomized trials evaluating primary surgical approaches followed by RT or CRT *vs* definitive CRT in treating stage III–IVA–B resectable OSCC; small-scale retrospective studies have reported conflicting results [6–9]. Furthermore, studies focusing on the efficacy of definitive CRT have evaluated all oral subsites as a whole, although the outcomes of OTSCC treatment differ from those reported for other subsites [10, 11]. To date, no studies have been reported to compare primary surgery followed adjuvant RT or CRT to definitive CRT alone in the management of advanced-stage resectable OTSCC patients.

The aim of the study was to compare the efficacy of definitive CRT to primary surgery followed by adjuvant RT or CRT in the treatment of stage III–IVA–B OTSCC.

MATERIALS AND METHODS

It is a retrospective analysis of the outcomes of 211 patients undergoing the treatment for stage III–IVA–B resectable OTSCC at the Department of Head and Neck Tumors of the National Cancer Institute between 2004 and 2013. The exclusion criteria were as follows: an unresectable tumor; early-stage disease (stage I or II); base of tongue tumors; a history of other malignancies; the presence of distant metastases; palliative treatment. The study was approved by the Ethics Committee of the National Cancer Institute.

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Abbreviations used: CRT – chemoradiation therapy; CI – confidence interval; cN – cervical lymph node involvement; cT – clinical extent of primary tumors; DFS – disease free survival; HR – hazard ratio; OS – overall survival; OSCC – oral squamous cell carcinoma; OTSCC — oral tongue squamous cell carcinoma; RT – radiotherapy; S-RT/CRT – surgical treatment followed by RT or CRT.

Tumors were staged according to the UICC TNM Classification of Malignant Tumors, 2009.

The patients were divided into two groups: 114 patients, who underwent the surgical treatment followed by adjuvant RT or CRT (S-RT/CRT), were included into the S-RT/CRT group; the definitive CRT group was composed of 97 patients. All patients in both groups received two-dimensional conventional RT.

The S-RT/CRT group underwent the surgical treatment, including a radical tongue resection, cervical lymph node dissection, and regional or free flap reconstruction of the tongue. The resection was done 1 cm distal to the visible margin of the tumor. Radical neck dissection or modified neck dissection was performed for the involved neck; supraomohyoid neck dissection was utilized for the clinically uninvolved neck. When the primary tumor extended beyond the midline of the tongue, bilateral neck dissection was employed. Adjuvant CRT was delivered for histologically confirmed high risk factors for recurrence, including positive resection margin where re-resection was not achievable or extranodal extension of nodal metastases was present. The adjuvant CRT protocol included: a course of RT delivered to the primary tumor bed at a total dose of 60 Gy (2 Gy/fraction) and to the sites of regional metastases at a dose of 40–60 Gy concurrent with intravenous (i/v) cisplatin 100 mg/m^2 every three weeks for 3 cycles. When dealing with intermediate-risk factors for relapse, including pT3, pT4, lymphovascular invasion, perineural invasion, lymph node involvement (pN 2–3), levels IV or V metastatic cervical lymph nodes, adjuvant RT was delivered to the primary tumor bed at a total dose of 60 Gy (2 Gy/fraction) and to the sites of regional metastases at a dose of 40–60 Gy.

In the CRT group, the treatment protocol included: RT to the primary tumor at a total dose of 66 Gy (2 Gy/fraction) and to the sites of regional metastases at a dose of 40–60 Gy concurrent with intravenous cisplatin 100 mg/m^2 every three weeks for 3 cycles. Where possible, patients having residual tumors or relapses of the disease received salvage surgery.

In patients of both groups, involved lymph nodes stations were treated with 60 Gy; uninvolved nodal stations were given 40 Gy. Overall survival (OS) and disease free survival (DFS) rates were compared between two groups. There was evaluated the prognostic effect of such variables as sex, age, clinical extent of primary tumors (cT), cervical lymph node involvement (cN), disease stage and treatment modality on OS and DFS. The incidence rates of low-jaw osteoradionecrosis were compared between the groups.

Statistical analysis of the results of the study was performed using the package MedCalc v. 18.11.3 (MedCalc Software bvba, Belgium, 1993–2018).

The mean value ($\bar{X}$) and standard deviation (SD) were calculated for the quantitative data. Frequency (%) was calculated for the qualitative data. When comparing the quantitative data between the two groups, the Student's *t*-test was employed (the data were consistent with normal distribution law); the chi-square test was used to compare the qualitative data. The survival analysis of was performed by the Kaplan — Meier method. Risk ratios (HRs) with 95% confidence intervals (95% CI) were calculated for OS and DFS. To evaluate the effect of several risk factors on survival (the calculation of adjusted HR), a Cox proportional hazards regression model was utilized. A stepwise method was used to select the independent factors of the multivariate models. *p* value less than 0.05 was considered statistically significant.

RESULTS

Two hundred and eleven patients met inclusion criteria. Table 1 summarizes overall characteristics of stage III–IVA–B resectable OTSCC patients. There were no statistically significant differences between age groups, sex, cT, cN, and disease stage ($p > 0.05$ for all comparisons).

In S-RT/CRT group, clear surgical resection margins were achieved in 106 (93%) patients; eight (7%) patients had involved surgical resection margins. All patients underwent neck dissection, including 44 (38.6%) of them having bilateral dissections. To have the tongue reconstructed, 64 (56.1%) patients were treated with a radial forearm free flap while the remaining 50 (43.9%) underwent pectoralis major myocutaneous flap reconstruction. Glossectomy without laryngeal preservation was performed in 12 (10.5%) patients. In S-RT/CRT patients, adjuvant RT was delivered at a median dose of 58.1 Gy (range 46–60 Gy). 79 (69.3%) patients received adjuvant RT, 35 patients (30.7%) had CRT. 29 (82.9%) out of 35 patients, who underwent CRT, received a cumulative cisplatin dose $\geqslant$ 200 mg /m^2.

CRT patients were delivered RT at an average dose of 60.4 Gy (range 54–66Gy). 83 (85.6%) out of 97 patients of this group received a cumulative

Table 1. Overall characteristics of stage III–IVA-B resectable OTSCC patients

Variable		S-RT/CRT group (n = 114)	CRT group (n = 97)	Significance level, *p*
Age, $\bar{X}$ ± SD, yr		56.4 ± 9.5	55.8 ± 9.8	0.64
Sex, n (%)	F	14 (12.3)	21 (21.6)	0.10
	M	100 (87.7)	76 (78.4)	
cT, n (%)	T2	8 (7.0)	12 (12.4)	0.28
	T3	75 (65.8)	65 (67.0)	
	T4	31 (27.2)	20 (20.6)	
cN, n (%)	N0	31 (27.2)	31 (32.0)	0.63
	N1	31 (27.2)	28 (28.9)	
	N2	51 (44.7)	36 (37.1)	
	N3	1 (0.9)	2 (2.0)	
Stage, n (%)	III	48 (42.1)	50 (51.5)	0.17
	IVA-B	66 (57.9)	47 (48.5)	

cisplatin dose ⩾ 200 mg/m². 19 (19.6%) CRT patients underwent salvage surgery.

The five-year OS was 57.0% in S-RT/CRT patients *vs* 20.4% in CRT group; the five-year DFS rates were 56.5% and 15.5% in S-RT/CRT and CRT groups, respectively. When evaluating the OS curves, statistically significant higher OS (*log-rank* test, $p < 0.001$) was revealed in S-RT/CRT patients as compared with that in the CRT group (HR = 0.33; 95% CI 0.23–0.47). While contrasting DFS curves, statistically significant higher DFS (log-rank test, $p < 0.001$) was also found in the S-RT/CRT group (HR = 0.25; 95% CI 0.17–0.37) (Fig. 1, 2).

Univariate Cox models were built to link clinical prognostic factors with OS and DFS (Table 2). Univariate analysis showed that prognostic factors having a statistically significant effect on OS included cT4 ($p = 0.03$), cN2 ($p < 0.001$), stage IVA-B ($p < 0.001$), and primary surgery followed by RT or CRT ($p < 0.001$) on OS. Sex and age were found to have no effect. There was revealed a statistically significant effect of cN2 ($p < 0.001$), stage IVA–B ($p < 0.001$) and primary surgery followed by RT or CRT ($p < 0.001$) on DFS. Sex, age, or cT were not associated with DFS.

We used the method of multivariate Cox model, to evaluate OS and DFS with respect to all clinical factors simultaneously. The stepwise acceptance-rejection method (critical rejection threshold was set at $p > 0.2$ and critical acceptance threshold was set at $p < 0.1$) was employed to select significant features. When performing multivariate analysis, cT4 ($p = 0.004$), cN2 ($p < 0.001$), cN3 ($p = 0.04$) and primary surgery followed by RT or CRT ($p < 0.001$) were found to have a statistically significant prognostic impact on OS. There was revealed a statistically significant prognostic effect of cT4 ($p = 0.02$), cN2 ($p < 0.001$), and primary surgery followed by RT or CRT ($p < 0.001$) on DFS. The findings of multivariate analysis are summarized in Table 3.

18 (15.8%) patients of S-RT/CRT group and 13 (13.4%) patients of CRT group ($p = 0.77$) developed mandibular osteoradionecrosis. In S-RT/CRT group, six patients had sequestrectomy and 12 patients underwent segmental resection of the mandible. In CRT group, sequestrectomy was performed in 5 patients; 8 patients had segmental resection of the mandible.

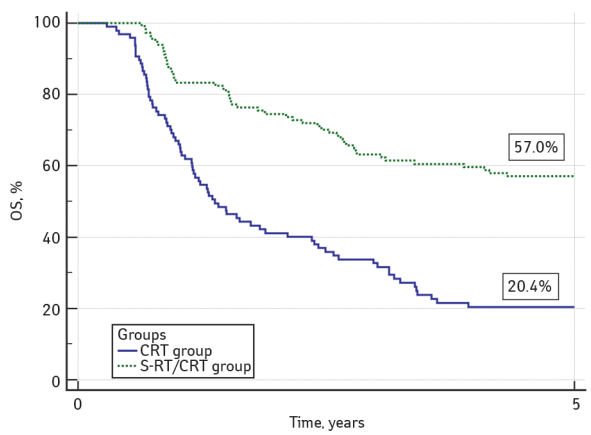

Fig. 1. Kaplan — Meier OS curves for S-RT/CRT group and definitive CRT group

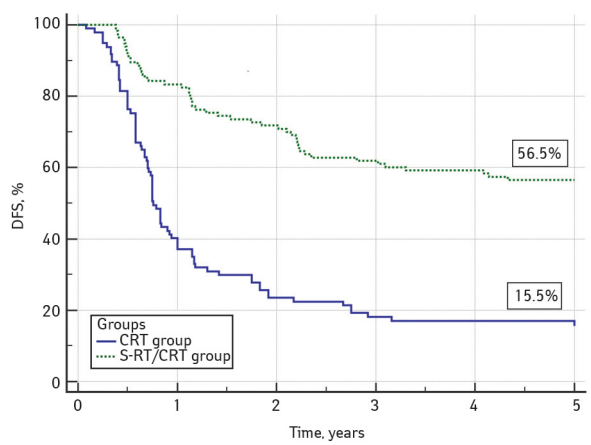

Fig. 2. Kaplan — Meier DFS curves for S-RT/CRT group and definitive CRT group

DISCUSSION

Treatment of advanced stage OSCC traditionally includes primary surgery followed by RT or CRT based on adverse prognostic factors. Recent studies have demonstrated promising outcomes when using non-surgical approaches in the treatment of patients with locally advanced laryngeal, hypopharyngeal, and oropharyngeal cancers [2–4]. However, only a few studies have addressed definitive CRT versus primary surgery followed by adjuvant RT or CRT in treating advanced stage OSCC, and the results of these studies are contradictory. Although the reconstructive surgical techniques have greatly improved, preserving the tongue using definitive CRT would significantly improve the functional outcomes of treatment and patients' quality of life. Therefore, in our opinion, it is important to know whether such a non-surgical approach is effective in advanced stage resectable OTSCC.

In our study, the five-year OS and DFS rates of patients with stages III–IVA–B resectable OTSCC, who underwent definitive CRT, were 20.4%, and 15.5%, respectively. Salvage surgery were performed in 16.5% of patients. In patients who had primary surgical treatment followed by adjuvant RT or CRT, the 5-year OS and DFS rates were 57.0% and 56.5%, respectively. There were found significantly higher 5-year OS and DFS rates in patients undergoing primary surgical treatment followed by adjuvant RT or CRT as compared with those in patients who had definitive CRT ($p < 0.001$ and $p < 0.001$, respectively).

Given that no studies have been reported evaluating the primary surgical approach followed by adjuvant RT or CRT *vs* definitive CRT in treating advanced-stage resectable OTSCC, we have analyzed the studies addressing these approaches in stage III–IV resectable OSCC. Stenson *et al*. [8] showed that 5-year overall and progression-free survival rates in stage III–IV OSCC patients who had definitive CRT were 66.9% and 65.9%, respectively; in patients who underwent surgical treatment followed by adjuvant CRT,

Table 2. Analysis of the effect of clinical prognostic factors on OS and DSF (univariate models of Cox proportional intensities)

Variable		DFS			OS		
		Coefficient of the model, b ± m	Significance of the coefficient difference from 0, p	HR (95% CI)	Coefficient of the model, b±m	Significance of the coefficient difference from 0, *p*	HR (95% CI)
Age, yr		0.0031 ± 0.0094	0.74	–	–0.0014 ± 0.0093	0.88	–
Sex	M				Ref		
	F	0.17 ± 0.23	0.45	–	0.23 ± 0.23	0.33	–
cT	T2				Ref		
	T3	0.22 ± 0.32	0.50	–	0.40 ± 0.35	0.26	–
	T4	0.53 ± 0.34	0.13	–	0.82 ± 0.37	0.03	2.3 (1.1–4.7)
cN	N0				Ref		
	N1	–0.02 ± 0.26	0.95	–	–0.06 ± 0.27	0.94	–
	N2	0.90 ± 0.22	< 0.001	2.5 (1.6–3.8)	1.00 ± 0.22	< 0.001	2.7 (1.8–4.2)
	N3	0.84 ± 0.73	0.25	–	1.16 ± 0.73	0.11	–
Stage	III				Ref		
	IVA-B	0.75 ± 0.18	< 0.001	2.1 (1.5–3.0)	0.93 ± 0.19	< 0.001	2.5 (1.7–3.7)
Treatment modality	Definitive CRT				Ref		
	S-RT/CRT	–1.25 ± 0.18	< 0.001	0.29 (0.20–0.41)	–1.05 ± 0.19	< 0.001	0.35 (0.24–0.50)

Table 3. Analysis of the effect of clinical prognostic factors on OS and DFS (multivariate models of Cox proportional intensities)

Variable		DFS			OS		
		Coefficient of the model, b ± m	Significance of the coefficient difference from 0, p	HR (95% CI)	Coefficient of the model, b ± m	Significance of the coefficient difference from 0, *p*	HR (95% CI)
cT	T2				Ref		
	T3	0.50 ± 0.33	0.14	–	0.72 ± 0.36	0.05	2.1 (1.0–4.2)
	T4	0.79 ± 0.35	0.02	2.2 (1.1–4.4)	1.11 ± 0.38	0.004	3.0 (1.4–6.4)
cN	N0				Ref		
	N1	0.04 ± 0.28	0.89	–	0.08 ± 0.28	0.78	–
	N2	1.30 ± 0.23	< 0.001	3.7 (2.3–5.7)	1.40 ± 0.23	< 0.001	4.0 (2.6–6.4)
	N3	1.11 ± 0.74	0.14	–	1.60 ± 0.76	0.04	4.9 (1.1–21.8)
Treatment modality	Definitive CRT				Ref		
	S-RT/CRT	–1.63 ± 0.20	< 0.001	0.20 (0.13–0.29)	–1.49 ± 0.20	< 0.001	0.23 (0.15–0.33)

5-year overall and progression-free survival rates were 53.0% and 53.6%, respectively. There were no statistically significant differences in overall and progression-free survival between groups. 18.4% of patients who underwent definitive CRT developed mandible osteoradionecrosis. It is not clear, however, whether the groups were comparable by disease stage and TNM. Quite high 5-year OS rate in the definitive CRT group could be explained by the inclusion of patients mostly with N0 and N1 regional lymph node status in this group, this information is not available in the study report, though.

Crombie *et al*. [6] evaluated the efficacy of definitive CRT in OSCC patients, but no comparison with the surgical approach and adjuvant RT or CRT was conducted. The authors reported that the 5-year OS and 5-year disease-specific survival rates of patients after definitive CRT were 29% and 30%, respectively. Salvage surgery was performed in 17% of patients. The rates of osteoradionecrosis and long-term feeding support among long-term survivors were 36% and 27%, respectively. It is noteworthy, however, that the 5-year OS in this study was 10% higher than in our study, which was associated with the inclusion of 11% of stage I–II patients in the study group. Scher *et al*. [12] also assessed the efficacy of definitive CRT in OSCC patients. The study found that the 5-year OS in patients after definitive CRT was 15%. A slightly lower OS rate compared to our result is probably due to the fact that patients with non-resectable oral tumors were included in the study group.

Iyer *et al*. [13] assessed primary surgery followed by RT versus definitive CRT in patients with stage III and IV squamous cell carcinoma of the head and neck. The study included patients with oral, oropharyngeal, laryngopharyngeal, laryngeal, and maxillary sinus cancers. Analysis of the entire cohort revealed no statistically significant difference in OS or disease-specific survival: 5-year rates were 45% *vs* 35% for OS ($p = 0.262$) and 56% *vs* 46% for disease-specific survival ($p = 0.637$) for the surgery and adjuvant RT group and definitive CRT group, respectively. However, in patients with oral cavity cancer, survival was significantly better in those who underwent primary surgery and adjuvant RT than that after CRT; the 5-year disease-specific survival rate was 68% *vs* 12%, respectively ($p = 0.038$) [13].

Elbers *et al*. [7] conducted a retrospective study comparing definitive CRT and primary surgery followed by adjuvant RT or CRT (after identification of factors of high risk for recurrence) in stage III–IV OSCC patients. It should be pointed out that there were statistically significant differences in disease stage and tumor size between the study groups. In the definitive CRT group, the 5-year OS was 22% and the 5-year DFS was 22%. In the surgery followed by adjuvant RT or CRT group, the 5-year OS was 45%, and the 5-year DFS was 45%. Comparison of OS and DFS curves revealed statistically significant higher OS and DFS in patients who underwent surgical treatment followed by adjuvant RT or CRT than in those who had definitive CRT ($p = 0.002$ and $p = 0.001$, respectively). 4% of patients who were treated with definitive CRT and 7% of patients undergoing surgery and adjuvant RT or CRT developed mandible osteoradionecrosis [7].

Thus, the results of our study differ from those reported by Stenson *et al*. [8] but they are comparable to those by Iyer *et al*. [13] and Elbers *et al*. [7], as we also established significantly higher 5-year OS and 5-year DFS rates in advanced OTSCC

patients who underwent surgical treatment with adjuvant RT or CRT, than in patients who received definitive CRT. Therefore, as of today, there is more evidence of the benefits of primary surgery followed by RT or CRT compared with definitive CRT, both for the treatment of stage III–IV OSCC in general and advanced-stage OTSCC patients in particular.

When conducting multivariate analysis of the data of stage III–IV A-B OTSCC patients, we revealed a statistically significant prognostic effect of the primary tumor extension cT4, cN, cN3 and treatment modality on OS and DFS. Elbers *et al*. [7] reported a statistically significant prognostic impact of age and the extension of the primary tumor on OS and DFS; the treatment modality was an independent prognostic factor for locoregional control.

Our study found a slightly higher incidence of mandibular osteoradionecrosis in the primary surgery followed by adjuvant RT or CRT group compared to that in the definitive CRT group (15.8 *vs* 13.4%), but the difference was not statistically significant. The true osteoradiosis rate in the definitive CRT group is likely to have been higher if the survival rates in this group were closer to those of the S-RT/CRT group. Overall, the incidence rate of mandible osteoradionecrosis in different studies varies from 5 to 36% [6, 7, 13–15].

To sum up, primary surgery with adjuvant RT or CRT in advanced-stage resectable OTSCC significantly increases five-year OS and DFS rates as compared to those after definitive CRT. The extension of primary tumor cT4, cN2, cN3 and the treatment modality were found to be among significant prognostic clinical factors in patients with stage III–IVA–B OTSCC. Further prospective studies addressing modern CRT and novel surgical techniques are needed.

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