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PROGNOSTIC FACTORS IN PATIENTS WITH SQUAMOUS CELL CARCINOMA OF THE ORAL TONGUE TREATED WITH ADJUVANT THERAPY FOLLOWING SURGERY

Valentina Krstevska[1] --- Snezhana Smichkoska[2] --- Beti Zafirova-Ivanovska[3]

[1]*Assistant Professor, Head of Department of Head and Neck Cancer, University Clinic of Radiotherapy and Oncology, Skopje, Republic of Macedonia*

[2]*Full Professor, Head of Department of Breast Cancer, University Clinic of Radiotherapy and Oncology, Skopje, Republic of Macedonia*

[3]*Full Professor, Director of the Institute of Epidemiology, Statistics and Informatics, Faculty of Medicine, Skopje, Republic of Macedonia*

ABSTRACT

Background. There is limited data on adjuvant treatment following surgery in patients with squamous cell carcinoma of the oral tongue. Aims. This retrospective study investigates prognostic value of different factors for local relapse-free survival (LRFS), regional relapse-free survival (RRFS), disease-free survival (DFS), and overall survival (OS) in patients with oral tongue cancer treated with adjuvant therapy following surgery. Materials and methods. Forty six patients with surgically treated oral tongue cancer were enrolled in the analysis. Adjuvant therapy consisted of postoperative radiotherapy (PO-RT) or postoperative concurrent chemoradiotherapy (PO-CCRT). All patients received three dimensional conformal radiotherapy. Weekly cisplatin was given as concurrent chemotherapy. Identification of prognostic factors for survival was done with univariate analysis. Multivariate analysis was used for factors confirmed as significant on univariate analysis. Results. Independent prognostic factors negatively influencing LRFS, DFS, and OS were ECOG performance status ($p = 0.002$, $p = 0.013$ and $p = 0.022$, respectively), overall stage ($p = 0.011$, $p = 0.010$ and $p = 0.009$, respectively), and pathologic nodal classification ($p = 0.016$, $p = 0.011$ and $p = 0.015$, respectively). Surgical margin status was an independent prognostic factor for RRFS, DFS, and OS ($p = 0.032$, $p = 0.027$ and $p = 0.028$, respectively). The type of adjuvant treatment used was independently prognostic for lower rates of LRFS and DFS ($p = 0.029$ and $p = 0.010$, respectively). Conclusions. Positive postoperative nodal status and close or positive resection margins had the most prominent negative prognostic influence on patients' survival.

Keywords: Oral tongue cancer, Postoperative radiotherapy, Postoperative concurrent chemoradiotherapy, Prognostic factors.

Contribution/ Originality

This study is one of very few studies which have investigated potential prognostic factors that might influence treatment outcome exclusively in patients with squamous cell carcinoma originating from the oral tongue whose adjuvant therapy following surgery consisted of postoperative radiotherapy or postoperative concurrent chemoradiotherapy.

1. INTRODUCTION

Squamous cell carcinoma of the oral tongue is a common head and neck cancer and represents the most common primary squamous cell carcinoma developing within the oral cavity [1, 2]. Carcinoma of the oral tongue has a great propensity to metastasize in the neck lymph nodes with level II being most frequently involved. Metastatic involvement of regional lymph nodes occurs in 10% to 40% of patients with T1-2 tumors [3-5]. The reported proportion of patients with T3 primaries presenting with pathologically positive lymph nodes revealed by selective neck dissection is between 56% and 70%. [6] Metastatic nodal disease has been recognized as a prognostic factor strongly associated with poor prognosis [7] resulting in 5-year survival rates of only 25% to 40% in patients with positive neck nodes [8]. The presence of extra capsular extension of neck lymph nodes metastasis as a reliable predictor of regional and distant recurrence impacts the further decrease of patients' survival [7, 9]. Additional recognized factors predicting poor prognosis include stage of disease, microscopically involved mucosal margins of resection, and perineural or lymphovascular invasion [10, 11].

Surgical excision of the primary tumor and elective or therapeutic neck dissection is the most frequently employed primary treatment in oral tongue cancer. It provides crucial information about the presence of high-risk histopathologic parameters, necessary for the guidance of correct planning of postoperative adjuvant therapy.

Postoperative radiotherapy (PO-RT) is a recommended adjuvant therapy for early stage oral tongue squamous cell carcinoma in patients with positive or close margins of resection and perineural or lymphovascular invasion [12]. For this patient's category, postoperative concurrent chemoradiotherapy (PO-CCRT) could also be potentially considered. The benefit of adjuvant concurrent chemoradiotherapy after radical surgery in high-risk squamous cell carcinoma of the head and neck including oral cavity cancers in terms of superior local control and disease-free survival rates compared with adjuvant radiotherapy alone has been demonstrated in two large-scale randomized trials conducted by Radiation Therapy Oncology Group (RTOG) and European Organization for Research and Treatment of Cancer (EORTC) [13, 14]. Extracapsular extension and positive margins were defined as high risk factors in both studies. In the comparative analysis of postoperative concurrent chemoradiotherapy trials of the RTOG (RTOG 9501) [13] and EORTC (EORTC 22931) [14], Bernier, et al. [15] suggested that adjuvant concurrent chemoradiotherapy should be used in the presence of extracapsular extension, microscopically

unclear margins, or both. The long-term follow-up of the RTOG 9501 trial also confirmed that significant improvements in locoregional control and DFS from concurrent chemoradiotherapy persisted in the subgroup that had extracapsular extension and/or involved margins [16].

Regarding the adjuvant therapy of advanced stage squamous cell carcinoma of the oral tongue, PO-RT should always be considered. PO-RT was also found to significantly improve the disease-free survival for early squamous cell carcinoma of the tongue with pathologic N1 disease in the retrospective study of Chen, et al. [17]. Besides the confirmed benefit for locoregional control, DFS and OS for patients with extracapsular extension or positive margins, a trend towards a survival benefit was found for patients with multiple metastatic lymph nodes, lymphovascular invasion, perineural invasion, and presence of low level neck nodes in patients with oral cavity/oropharynx primaries [15].

We designed our retrospective study to investigate the prognostic impact of different factors on survival in patients with squamous cell carcinoma of the oral tongue presenting with one or more unfavorable pathologic features treated with radiotherapy with or without concurrent chemotherapy adjuvant to primary surgery.

2. MATERIALS AND METHODS

Our retrospective study presents the results of postoperative adjuvant treatment in patients with squamous cell carcinoma of the oral tongue. Between March 2006 and December 2011, 46 patients with surgically treated oral tongue cancer underwent postoperative adjuvant therapy at the University Clinic of Radiotherapy and Oncology in Skopje. Early stage disease (I and II) was present in 20 patients (43.5%). The remaining 26 patients (56.5%) had an advanced stage disease (III and IVA). The study was approved by the Institutional Review Board. All patients were free of distant metastases, as determined by a complete medical history, physical examination, chest X-ray, liver ultrasound, complete blood cell count, and basic blood chemistry. Tumor staging was based on the pathology findings according to the AJCC staging criteria for the given time period [18, 19].

2.1. Patient Characteristics

Patient characteristics are listed in Table 1. The median patient age was 57 years (range, 39-77 years), 82.6% of patients were men, and ECOG performance status 0 at presentation was recorded in 36 patients (78.3%). Noxious factors as cigarette smoking and alcohol consumption were noticed in 80.4% and 65.2% of patients, respectively.

2.2. Surgery

Wide excision of the primary tumor was the most commonly employed surgical procedure realized in 37 patients (80.4%). Partial glossectomy was performed in 7 patients (15.2%), and hemiglossectomy in only 2 patients (4.4%). Forty patients underwent simultaneous neck dissection. Supraomohyoid neck dissection was performed in 22 patients (55.0%), modified radical neck dissection was realized in 16 patients (40.0%), and 2 patients (5.0%) underwent bilateral

modified radical neck dissection. In the 6 patients with clinically negative lymph neck nodes (cN0) who did not undergo neck dissection, computed tomography (CT) scanning and/or magnetic resonance imaging (MRI) of the neck region was mandatory prior to adjuvant therapy commencement in order to provide imaging studies confirmation of the negative neck nodal status.

Tumor characteristics revealed upon histopathologic examination are given in Table 2. In one half of the patients primary oral tongue cancer was classified as pT2. Nodal disease (pN1 and pN2) was determined in one half of the patients who underwent neck dissection. Surgical margins were microscopically close (≤ 4 mm) or positive in 21 patients (45.7%). Extracapsular extension was confirmed in 8 out of 20 patients with metastatic nodal disease (40.0%).

2.3. Adjuvant Therapy

Adjuvant therapy consisted of PO-RT or PO-CCRT. Adjuvant PO-RT was administered in patients with stage I and II disease who had pathologic factors associated with high risk of local recurrence including lymphovascular and perineural invasion. Adjuvant radiotherapy was also used in patients with stage III or IVA disease who had no evidence of positive or close resection status and other negative pathologic findings and, in cases with positive pathologic lymph node status, who had no more than two positive lymph nodes without extracapsular spread. PO-CCRT was realized for stage I and II disease in the presence of close or positive surgical margins. It was also administered for stage III and IVA disease when there were present close or positive margins of resection, lymphovascular and perineural invasion, more than two metastatic lymph nodes, and evidence of extracapsular extension. Table 3 shows the adjuvant treatment employed in accordance with the stage of disease.

Radiotherapy was performed on a linear accelerator using three dimensional conformal radiotherapy with conventional fractionation of 2 Gy per fraction, 1 fraction per day, 5 fractions per week. The high-risk planning target volume (PTV60) was defined as the region of the resected primary tumor in patients without positive or close margins of resection, as well as the dissected areas of the neck with pathologically one or two positive lymph nodes without extracapsular extension plus a margin of 0.5 cm. The high-risk PTV66 enclosed the bed of the primary tumor in cases with positive or close margin status and the dissected region of the neck with pathologically proven metastases in more than two lymph nodes and/or revealed extracapsular nodal spread plus a margin of 0.5 cm. The PTV50 encompassed lymph nodes in the neck that were to be electively irradiated according to the proposal for the delineation of the nodal CTV in the post-operative neck [20] plus a margin of 0.5 cm, and also included the high-risk PTV.

The median time interval between surgery and the beginning of radiotherapy for the whole group of patients was 7.4 weeks (range, 4 to 7 weeks). Postoperative radiotherapy was continued for a median time of 6 weeks (range, 6-7 weeks), and the median time for postoperative concurrent chemoradiotherapy was 7 weeks (range 6.5-7 weeks). All patients received the prescribed dose of radiation.

Patients treated with PO-CCRT received cisplatin given on a weekly basis (30 mg/m^2), starting at the first day of adjuvant radiotherapy. The majority of patients (73.3%) received all six cycles of chemotherapy. The median total dose of cisplatin given was 280 mg/m^2 (range, 200-300 mg/m^2).

2.4. Statistical Analysis

Follow-up time was calculated from the start of adjuvant treatment until the date of last follow-up or death. Local relapse-free survival (LRFS) and regional relapse-free survival (RRFS) were calculated from the date of adjuvant treatment start to the date of diagnosis of local or regional recurrence, respectively, or to the date of more recent follow-up visit. Disease-free survival (DFS) was measured from the date of adjuvant therapy commencement to the date of diagnosis of local, regional, or distant relapse, or to the date of the last follow-up. Overall survival (OS) was calculated from the beginning of adjuvant therapy to the last follow-up visit or to the date of death. The endpoint for OS was death from all causes. The Kaplan-Meier method was used to create the survival curves [21]. To identify prognostic factors for survival, the following variables were subjected to univariate analysis: gender, age, ECOG performance status, tobacco consumption, alcohol consumption, overall stage, pathologic tumor classification (pT), pathologic nodal classification (pN), grade of differentiation, surgical margin status, lymphovascular invasion, perineural invasion, extracapsular nodal extension, and the type of adjuvant treatment. Differences between the actuarial curves were tested by the log-rank test. Factors that were significant on univariate analysis were assessed by multivariate analysis using a Cox regression model and the log-rank test. Statistical significance was defined as p less than 0.05.

3. RESULTS

The follow-up for all patients was 33.3 months (range, 9-82 months). The follow-up for living patients was 45.4 months (range, 18-82 months), and the follow-up for dead patients was 15.3 months (range, 9-36 months). The 3-year LRFS, RRFS, DFS, and OS rates for all patients were 62.8%, 80.2%, 57.7%, and 59.8%, respectively [Figure 1].

3.1. Patterns of Failure

At the time of analysis 26 patients were alive without known recurrent disease and one patient was alive with a regional recurrence treated with salvage surgery 44 months following adjuvant therapy start. Recurrent disease was developed in 20 patients (43.5%), including 9 local recurrences, 7 locoregional recurrences, 3 regional recurrences, and only 1 distant recurrence.

3.2. Univariate Analysis

The impact of patients, tumors and treatment related parameters on LRFS, RRFS, DFS, and OS analyzed by univariate analysis are presented in Table 4 and Table 5.

Univariate analysis indicated that LRFS was significantly influenced by ECOG performance status 1 (0 better than 1, p = 0.0004), alcohol status (absent better than present, p = 0.0314),

overall stage (I-II better than III-IVA, p = 0.0024) [Figure 2], pathologic tumor classification (pT1 better than pT2-3, p = 0.0215), pathologic nodal classification (pN0 better than pN+, p = 0.0078), grade of differentiation (well and moderate better than poor, p = 0.0008), and extracapsular extension (absent better than present, p <0.0001). The ECOG performance status (0 better than 1, p = 0.0490), pathologic nodal classification (pN0 better than pN+, p = 0.0195), margins of resection (negative better than close or positive, p = 0.0155), and extracapsular nodal spread (absent better than present, p = 0.0113) were significantly associated with RRFS [Table 4].

Prognostic factors with significant negative impact on both DFS and OS were ECOG performance status 1 (p = 0.0074 for DFS, and p = 0.0157 for OS), positive alcohol status (p = 0.0154 for DFS, and p = 0.0258 for OS), overall stage III-IVA (p = 0.0043 for DFS, and p = 0.0036 for OS), positive pathologic nodal classification (pN+) (p = 0.0052 for DFS, and p = 0.0085 for OS), poor grade of differentiation (p = 0.0034 for DFS, and p = 0.0043 for OS), positive or close margins of resection (p = 0.0184 for DFS, and p = 0.0183 for OS), and presence of extracapsular extension (p <0.0001 for DFS, and p = 0.0022 for OS) [Table 5]. Univariate analysis also indicated that PO-CCRT was significantly associated with lower 3-year rates of LRFS, RRFS, DFS, and OS (p = 0.0130; p = 0.0101; p = 0.0025, and p = 0.0052, respectively).

3.3. Multivariate Analysis

The results of multivariate analysis of prognostic factors revealed as significant for LRFS and RRFS in the univariate analysis are shown in Table 6. Independent prognostic factors with negative influence on LRFS were ECOG performance status (1 vs. 0, p = 0.002), overall stage (III-IVA vs. I-II, p = 0.011), pathologic nodal classification (pN+ vs. pN0, p = 0.016), and the type of adjuvant treatment used (PO-CCRT vs. PO-RT, p = 0.029). Surgical margin status was found as the only independent prognostic factors negatively influencing RRFS (close or positive vs. negative, p = 0.032). The results of multivariate analysis of prognostic factors confirmed as significant for DFS and OS in the univariate analysis are shown in Table 7. Independent prognostic factors for inferior both DFS and OS were ECOG performance status (1 vs. 0, p = 0.013 for DFS, and p = 0.022 for OS), overall stage (III-IVA vs. I-II, p = 0.010 for DFS, and p = 0.009 for OS), pathologic nodal classification (pN+ vs. pN0, p = 0.011 for DFS, and p = 0.015 for OS), and surgical margin status (close or positive vs. negative, p = 0.027 for DFS, and p = 0.028 for OS). Alcohol consumption (present vs. absent, p = 0.046), and the type of adjuvant treatment (PO-CCRT vs. PO-RT, p = 0.010) were independently prognostic for lower rates of DFS only.

4. DISCUSSION

The mainstay of treatment for oral cancer including squamous cell carcinoma of the oral tongue is usually surgery [22]. Radiotherapy with or without chemotherapy is employed as adjuvant to primary surgery in order to enhance locoregional control for cases with unfavorable pathological features [23]. In the study of [1] conducted on 50 patients with squamous cell carcinoma of the oral tongue, the reported standard treatment approach at the University of

Colorado Denver consisted of surgical resection in patients with resectable disease followed by adjuvant radiotherapy or chemoradiotherapy. High-risk pathologic features included close or positive margins, tumor larger than 4 cm, deep invasion, lymphovascular invasion, perineural invasion, and positive lymph nodes. The most commonly used concurrent chemotherapy regimen given in 70% of patients was weekly carboplatin and paclitaxel.

At the Princess Margaret Hospital, the high-risk pathologic features in patients with oral tongue squamous cell carcinoma who underwent surgery and adjuvant postoperative radiotherapy were advanced tumor stage and positive neck nodes, positive margins of resection and extranodal extension. Postoperative concurrent chemoradiotherapy was used in only one patient with positive margins of resection and extranodal extension [24]. In the retrospective study of Tai, et al. [25] on 190 patients with T1-2 oral tongue cancer who underwent surgery as the primary treatment, postoperative adjuvant chemoradiotherapy was performed in 38 patients (20.0%) for inadequate surgical margin, multiple neck node metastasis, or extracapsular spread.

In the current study, adjuvant therapy consisting of PO-RT was used in 11 patients (23.9%) with early stage disease (I-II) who had pathologically determined lymphovascular invasion and/or perineural invasion, and in 5 patients (10.9%) with stage III-IVA disease without negative patologic findings including those with no more than two positive lymph nodes without extracapsular extension. More aggressive adjuvant treatment approach consisting of PO-CCRT was used in 9 patients (19.6%) with stage I-II disease with close or positive margins of resection, and in 21 patients (45.6%) with advanced stage disease (III-IVA) with pathologically revealed close or positive margins of resection, lymphovascular invasion, perineural invasion, presence of more than two metastatic lymph nodes in the neck and extracapsular extension of the nodal disease.

Based on the results of RTOG 9501 and EORTC 22931 trials [13, 14], and the results of their comparative analysis [15], as well as on the results of the long-term follow-up of the RTOG 9501 trial [16], PO-CCRT is recently adopted as recommended adjuvant treatment option for patients with high-risk head and neck cancer presenting with extracapsular nodal spread and/or involved surgical margins.

The multivariate model in our study revealed ECOG performance status as a prognostic factor with ECOG performance status 1 negatively influencing LRFS, DFS, and OS. Advanced overall stage (III-IVA) had also negative impact on LRFS, DFS, and OS. On the univariate analysis employed in the study of Fan, et al. [26] patients with stage IV disease had a significantly worse recurrence-free survival, but on the multivariate analysis, the stage was found to be no longer significant.

In our study, pathologic nodal classification was revealed as an independent prognostic factor indicating that patients with positive nodal status had significantly worse LRFS, DFS, and OS. These results are similar to the results of the multivariate analysis in the study of Ganly, et al. [27]. In this study, the pathologic neck status was an independent predictor of LRFS, recurrence-free survival, disease-specific survival, and OS. The authors reported that patients who had pN2b neck status had an increased risk of developing recurrent disease, and an increased risk of dying

compared to patients who had N0 neck status. Multiple lymph node metastases were also confirmed as an independent negative prognostic factor for recurrence-free survival in the study of Fan, et al. [26]. Greenberg, et al. [7] confirmed that patients with two or more pathologically positive lymph nodes had worse DFS and OS. Other authors reported the significant decrease in survival in patients with nodal disease at the time of initial treatment [11, 28]. Hence, Nyman, et al. [28] reported that the 5-year OS of patients with N0 was 50.0% compared to 11.0% for patients with N-positive necks (N1-N3).

Mulivariate analysis in our study confirmed the negative influence of close or positive surgical margin status on RRFS, DFS, and OS. These results correspond with the results reported by other authors [11, 29]. Sessions, et al. [11] reported that disease-specific survival was significantly worsened in patients with close or involved margins when compared with clear margins of resection. Analyzing the impact of surgical margin status and the use of an interstitial implant on patients with T1-T2 oral tongue cancers following surgery, Chao, et al. [29] reported statistically similar rates of local control and OS for patients with positive margins who were treated with postoperative radiotherapy compared with patients who had negative margins of resection. Although the presence of extracapsular extension in our study was found as a significant prognostic factor on the univariate analysis with a negative influence on LRFS, RRFS, DFS, and OS, on the multivariate analysis it did not remain significant. In the retrospective analysis of the extent of extracapsular spread of the nodal disease in the neck in patients with cancer of the oral tongue, Greenberg, et al. [7] showed a significant increase of the recurrence rate as a consequence of increased number of positive nodes with extracapsular extension. Positive extracapsular spread was found as a negative prognostic factor for recurrence-free survival and overall survival on the multivariate analysis in the study of Fan, et al. [26].

The unexpected result on the multivariate analysis in our study was PO-CCRT revealed as independent prognostic factor negatively influencing LRFS and DFS. On contrary, in the retrospective study of 201 patients with advanced stage oral tongue cancer of Fan, et al. [26], multivariate analysis showed that concurrent chemoradiotherapy with cisplatin-based regimens was a significant independent prognostic factor with positive impact on recurrence-free survival and OS. One possible explanation of the finding in our study could be the regimen of concurrent weekly cisplatin. Given that PO-CCRT was used not only for patients with close or positive margins of surgical resection or the presence of extracapsular extension of the nodal disease in the neck, but also in the patients with lymphovascular invasion, perineural invasion, and the presence of more than two metastatic lymph nodes in the neck, it can be assumed that this patient category has a very high probability for locoregional recurrence. Therefore, the dose of concurrent cisplatin proposed by RTOG 9501 trial [13] and EORTC 22931 trial [14] i.e. 100 mg/m2 administered at days 1, 22, and 43 of postoperative radiotherapy could be presumed as an option for achievement of better results regarding locoregional control and survival.

It should also be mentioned that there is a small number of studies focused on analysis of prognostic factors in patients with oral tongue squamous cell carcinoma treated with adjuvant radiotherapy or concurrent chemoradiotherapy following surgery. However, according to the

available data, positive pathologic nodal status, close or positive margins of resection and the presence of extracapsular extension were revealed as the most frequent negative prognostic factors. The multivariate analysis in our study also pointed out the negative influence of the positive postoperative nodal status on LRFS, DFS, and OS. In the current study, close or positive resection margins were confirmed as prognostic factors negatively influencing RRFS, DFS, and OS. Unexpectedly, extracapsular extension of the nodal disease was not found to be an independent factor for either LRFS, RRFS, DFS, or OS.

5. CONCLUSIONS

Taking into account the results of our study and the data from the literature, we can conclude that pathologic nodal classification and surgical margin status are the most important prognostic factors in patients with oral tongue cancer treated with surgery and adjuvant radiotherapy or chemoradiotherapy. Although the role of extracapsular extension as a prognostic factor was not confirmed in the current study, based on the results from all the studies revealing it as an independent prognostic variable, we have to emphasize its significant prognostic relevance. We also have to point out that prospective randomized studies conducted exclusively on oral tongue cancer comparing the results of PO-CCRT for patients with close or positive margins of resection and extracapsular extension with those achieved with PO-CCRT for patients with close or positive margins of resection, lymphovascular invasion, perineural invasion, presence of more than two metastatic lymph nodes in the neck and extracapsular extension of the nodal disease should be considered highly recommendable.

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Table-1. Patients characteristics

Characteristics	**No. of patients**	**%**
Gender		
Male	38	82.6
Female	8	17.4
Median age, years (range)	57 (39-77)	
Age (years)		
< 60	23	50.0
≥ 60	23	50.0
Performance status (ECOG)		
0	36	78.3
1	10	21.7
Tobacco consumption		
Absent	9	19.6
Present	37	80.4
Alcohol consumption		
Absent	16	34.8
Present	30	65.2

Abbreviations: ECOG, Eastern Cooperative Oncology Group.

Table-2. Pathologic tumor characteristics

Characteristics	No. of patients	%
Pathologic tumor classification (pT)		
pT1	10	21.7
pT2	23	50.0
pT3	13	28.3
Pathologic nodal classification (pN), n=40		
pN0	20	50.0
pN1	6	15.0
pN2	14	35.0
Grade of differentiation		
Well	6	13.0
Moderate	26	56.5
Poor	14	30.5
Surgical margin status		
Negative	25	54.3
		Continue
Close/positive	21	45.7
Lymphovascular invasion		
Absent	19	41.3
Present	27	58.7
Perineural invasion		
Absent	23	50.0
Present	23	50.0
Extracapsular nodal extension, n=20		
Absent	12	60.0
Present	8	40.0

Table-3. Adjuvant therapy according to stage of disease (n=46)

Adjuvant therapy	Number of patients by stage (%)		Total
	I-II	III-IVA	
PO-RT	11 (23.9)	5 (10.9)	16 (34.8)
PO-CCRT	9 (19.6)	21 (45.6)	30 (65.2)
Total	20 (43.5)	26 (56.5)	46 (100.0)

Abbreviations: PO-RT, postoperative radiotherapy; PO-CCRT, postoperative concurrent chemoradiotherapy.

Table-4. Prognostic factors for local relapse free-survival and regional relapse-free survival: univariate analysis

Variable	No. of patients	3-year LRFS, %	p-value for LRFS	3-year RRFS, %	p-value for RRFS
Gender					
Male	38	63.2	0.7227	81.4	0.6811
Female	8	72.6		87.4	
Age (years)					
< 60	23	64.3	0.8587	66.9	0.2984
≥ 60	23	65.8		78.3	
Performance status (ECOG)					
0	36	75.3	**0.0004**	88.8	**0.0490**
1	10	29.7		57.7	
Tobacco consumption					
Absent	9	76.3	0.5232	88.9	0.5447
Present	37	62.2		80.9	
Alcohol consumption					
Absent	16	86.5	**0.0314**	93.6	0.1234
Present	30	52.7		76.4	
Overall stage					

I-II	20	89.3	**0.0024**	95.1	0.1007
III-IVA	26	46.4		72.5	
Pathologic tumor classification					
pT1	10	100.0	**0.0215**	90.0	0.4662
pT2-3	36	56.2		80.3	
Pathologic nodal classification					
pN0	20	76.7	**0.0078**	95.0	**0.0195**
pN+	20	47.4		68.9	
Histologic grade of differentiation					
Well	6	74.8	**0.0008**	83.3	0.5063
Moderate	26	83.8		88.5	
Poor	14	24.1		69.7	
Surgical margin status					
Negative	25	70.6	0.2960	91.6	**0.0155**
Positive/close	21	57.9		71.4	
Lymphovascular invasion					
Absent	19	64.2	0.6750	77.3	0.2496
Present	27	65.3		89.3	
Perineural invasion					
Absent	23	60.6	0.7665	82.6	0.7240
Present	23	68.4		82.6	
Extracapsular nodal extension					
Absent	12	72.1	**<0.0001**	91.8	**0.0113**
Present	8	0		0	
Type of adjuvant treatment					
PO-RT	16	85.8	**0.0130**	100.0	**0.0101**
PO-CCRT	30	53.3		72.9	

Abbreviations: LRFS, local relapse-free survival; RRFS, regional relapse-free survival; PO-RT, postoperative radiotherapy; PO-CCRT, postoperative concurrent chemoradiotherapy.

Table-5. Prognostic factors for disease free-survival and overall survival: univariate analysis

Variable	No. of patients	3-year DFS, %	p-value for DFS	3-year OS, %	p-value for OS
Gender					
Male	38	59.1	0,9228	59.2	0,9440
Female	8	62.4		62.5	
Age (years)					
< 60	23	60.1	0.8732	60.7	0.9194
≥ 60	23	59.1		57.4	
Performance status (ECOG)					
0	36	68.4	**0.0074**	67.8	**0.0157**
1	10	29.7		29.7	
Tobacco consumption					
Absent	9	66.6	0.7671	66.6	0.7567
Present	37	58.3		58.3	
Alcohol consumption					
Absent	16	82.3	**0.0154**	82.3	**0.0258**
Present	30	46.8		46.8	
Overall stage					
I-II	20	85.0	**0.0043**	84.7	**0.0036**
III-IVA	26	40.4		41.6	
Pathologic tumor classification					
pT1	10	89.9	0.0578	90.3	0.0615
pT2-3	36	51.8		52.3	
Pathologic nodal classification					
pN0	20	72.2	**0.0052**	76.6	**0.0085**

pN+	20	39.3		34.7	
Histologic grade of differentiation					
Well	6	62.8	**0.0034**	55.8	**0.0043**
Moderate	26	80.8		76.8	
Poor	14	21.3		28.2	
Surgical margin status					
Negative	25	70.6	**0.0184**	73.4	**0.0183**
Positive/close	21	47.0		47.0	
Lymphovascular invasion					
Absent	19	57.0	0.9412	61.2	0.7912
Present	27	63.1		59.1	
Perineural invasion					
Absent	23	51.4	0.4115	49.3	0.3605
Present	23	68.2		69.2	
Extracapsular nodal extension					
Absent	12	65.3	**<0.0001**	58.4	**0.0022**
Present	8	0		0	
Type of adjuvant treatment					
PO-RT	16	85.5	**0.0025**	82.8	**0.0052**
PO-CCRT	30	45.4		46.5	

Abbreviations: DFS, disease-free survival; OS, overall survival; PO-RT, postoperative radiotherapy; PO-CCRT, postoperative concurrent chemoradiotherapy.

Table-6. Prognostic factors for local relapse free-survival and regional relapse-free survival: multivariate analysis.

	LRFS		**RRFS**	
Variable	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Performance status (ECOG):				
1 vs. 0	5.05 (1.85-13.76)	**0.002**	3.44 (0.91-12.85)	0.067
Alcohol consumption:				
present vs. absent	4.32 (0.98-19.05)	0.053	/	/
Overall stage:				
III-IVA vs. I-II	6.94 (1.57-30.59)	**0.011**	/	/
Pathologic tumor classification:				
pT2-3 vs. pT1	31.03 (0.23-416.89)	0.169	/	/
Pathologic nodal classification:				
pN+ vs. pN0	4.12 (1.30-13.07)	**0.016**	8.07 (0.99-65.82)	0.051
Grade of differentiation:				
poor vs. well	1.24 (0.14-10.59)	0.846	/	/
poor vs. moderate	6.98 (0.89-54.87)	0.065	/	/
Surgical margin status:				
close or positive vs. negative	/	/	5.44 (1.15-25.65)	**0.032**
Extracapsular nodal extension:				
present vs. absent	1.57 (0.39-6.29)	0.523	1.14 (0.19-6.85)	0.884
Type of adjuvant treatment:				
PO-CCRT vs. PO-RT	0.19 (0.04-0.85)	**0.029**	0.02 (0.00-4.23)	0.155

Abbreviations: LRFS, local relapse-free survival; RRFS, regional relapse-free survival; HR, hazard ratio; 95% CI, 95% confidence interval; PO-CCRT, postoperative concurrent chemoradiotherapy; PO-RT, postoperative radiotherapy.

Table-7. Prognostic factors for disease free-survival and overall survival: multivariate analysis

	DFS		OS	
Variable	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Performance status (ECOG):				
1 vs. 0	3.32 (1.29-8.58)	**0.013**	3.01 (1.17-7.75)	**0.022**
Alcohol consumption:				
present vs. absent	3.50 (1.02-11.95)	**0.046**	3.24 (0.94-11.15)	0.062
Overall stage:				
III-IVA vs. I-II	4.30 (1.42-13.03)	**0.010**	5.15 (1.50-17.74)	**0.009**
Pathologic nodal classification:				
pN+ vs. pN0	3.86 (1.37-10.94)	**0.011**	3.64 (1.29-10.28)	**0.015**
Grade of differentiation:				
poor vs. well	0.76 (0.16-3.68)	0.764	0.70 (0.14-3.47)	0.662
poor vs. moderate	3.43 (0.75-15.64)	0.112	3.14 (0.69-14.25)	0.137
Surgical margin status:				
close or positive vs. negative	2.83 (1.13-7.13)	**0.027**	2.85 (1.12-7.27)	**0.028**
Extracapsular nodal extension:				
present vs. absent	2.26 (0.61-8.41)	0.226	2.18 (0.59-8.14)	0.245
Type of adjuvant treatment:				
PO-CCRT vs. PO-RT	0.15 (0.043-0.64)	**0.010**	0.16 (0.04-0.70)	0.155

Abbreviations: DFS, disease-free survival; OS, overall survival; HR, hazard ratio; 95% CI, 95% confidence interval; PO-CCRT, postoperative concurrent chemoradiotherapy; PO-RT, postoperative radiotherapy.

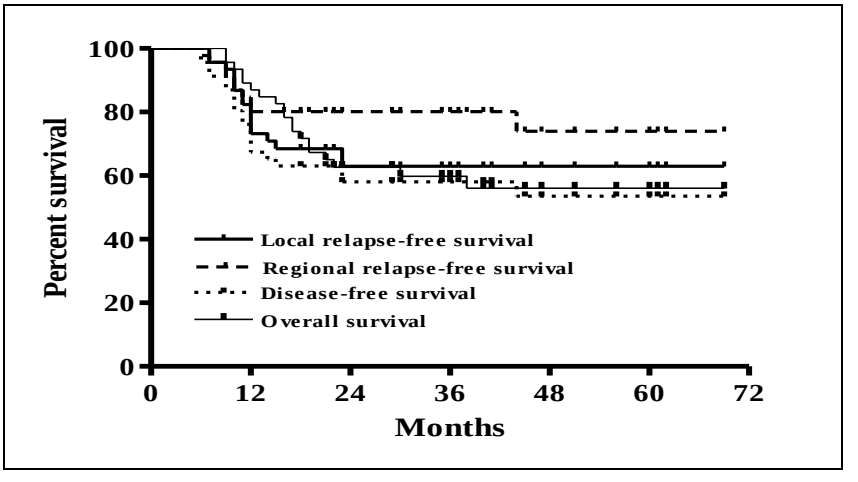

Figure-1. Local relapse-free survival, regional relapse-free survival, disease-free survival, and overall survival are illustrated for total number patients.

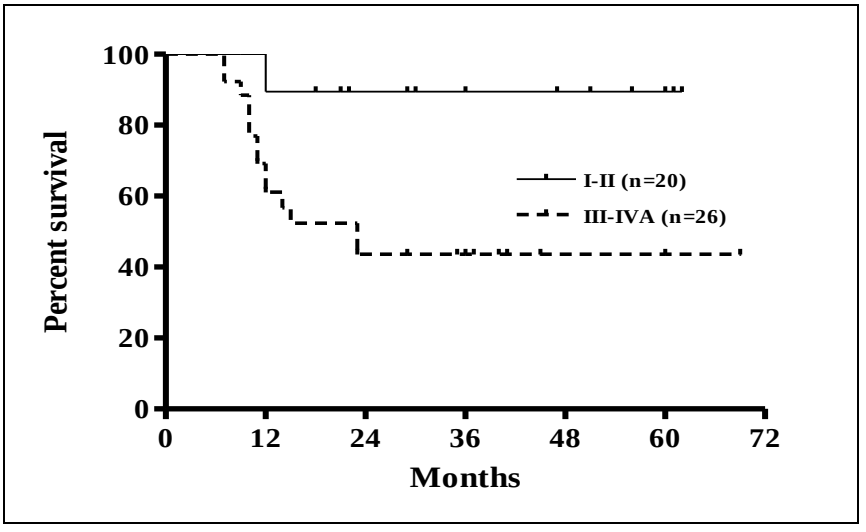

Figure-2. Local relapse-free survival according to overall stage (Kaplan- Meier estimates). Log-rank test; chi-square = 9.216; p = 0.0024.

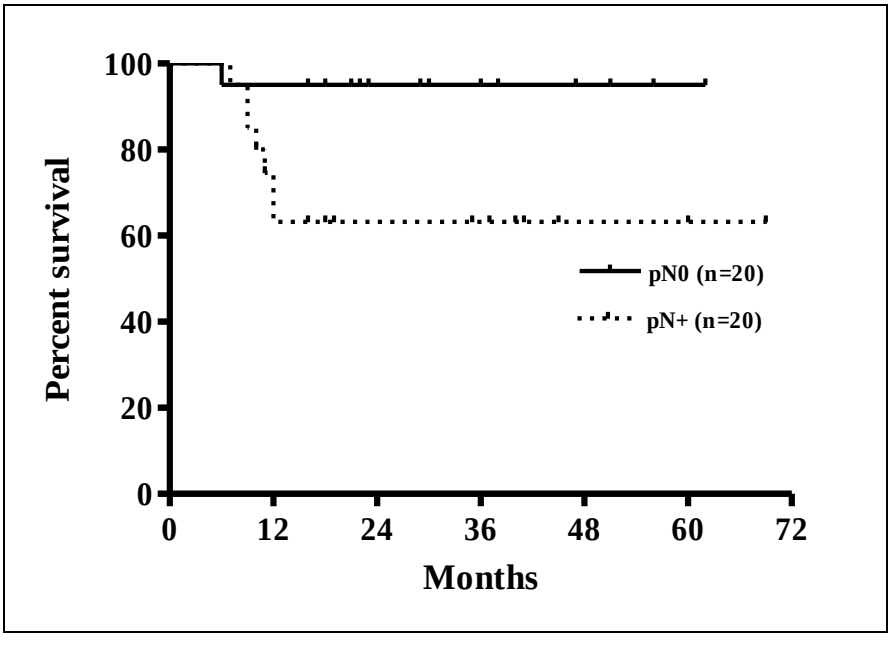

Figure-3. Regional relapse-free survival according to pathologic nodal classification (Kaplan- Meier estimates). Log-rank test; chi-square = 5.457; p = 0.0195.

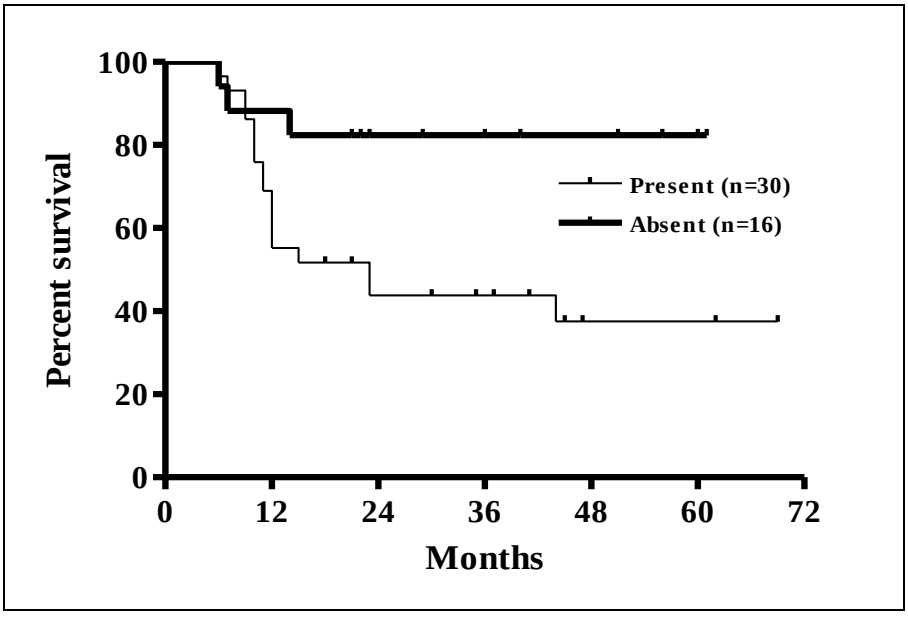

Figure-4. Disease-free survival according to alcohol consumption (Kaplan- Meier estimates). Log-rank test; chi-square = 5.872; p = 0.0154.

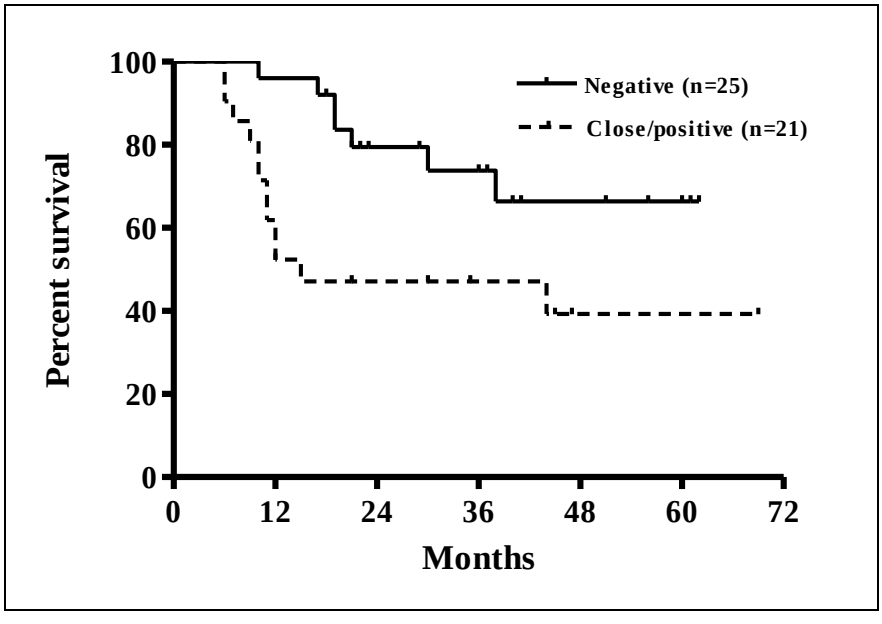

Figure-5. Overall survival according to surgical margin status (Kaplan- Meier estimates). Log-rank test; chi-square = 5.569; p = 0.0183.