Advanced carcinoma of the oropharynx: survival analysis comparing two treatment modalities

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Abstract: About 92,000 new cases of oropharynx carcinoma are expected to occur annually worldwide. There is no consensus about the best therapy for these advanced tumors. The objective of the present study was to evaluate overall and disease-free survival rates of patients with advanced oropharynx squamous cell carcinoma, comparing surgery + radiotherapy with chemotherapy + radiotherapy. Medical records of patients were reviewed. Previously treated tumors were excluded. Clinical, demographic and microscopic information was collected, and p16 staining was performed. Kaplan-Meier survival curves were plotted. Forty-seven cases were included, 41 men and 6 women, having a mean age of 56.3 years. Most patients were smokers (85.1%) and consumed alcohol (74.5%). Patients were stage III (21.3%) or IV (78.7%). Most lesions affected the base of the tongue (36.2%). Of the 23 cases available for p16 testing, 3 were positive (13.0%). There was no difference between the overall and the disease-free survival rates for the two treatment modalities (p>0.05), even when only resectable tumors were compared. Seventeen cases experienced recurrence (36.2%); 16 (34.0%) patients remained alive without disease; 15 (31.9%) died due to disease; 9 (19.2%) were recurrent at the last follow-up. The two treatment protocols were equally efficient in treating advanced oropharynx squamous cell carcinoma, since both promoted similar overall and disease-free survival rates. The results and interpretations related herein mostly regard "conventional" oropharyngeal squamous cell carcinomas, as opposed to HPV-associated tumors.

Keywords: Oropharynx; Oropharyngeal Neoplasms; Carcinoma, Squamous Cell; Therapeutics; Survival.

Introduction

The oropharynx encompasses soft palate, tonsils, base of tongue, uvula, pharynx wall and vallecula.[1,2]. Oropharynx squamous cell carcinoma (OP-SCC) had an annual global incidence of 92,887 cases and 51,005 deaths worldwide[3] in 2018. Men are more affected than women, usually in the 5th to 7th decades of life.[4] The most relevant etiological factors are smoking habit, alcohol consumption[4] and human papilloma virus (HPV).[5,6,7] Clinical staging of the tumors is based on the TNM classification system.[8,9] There is no consensus regarding the treatment of advanced cases of the disease.

First line treatment should include surgery (Surg) and radiotherapy (RT), when clear margins can be achieved with surgery,[10,11] or else platinum-based chemoradiation (CT+RT).[2,12]

Disease control depends on the extension and site of the primary tumor, but neck involvement is the major prognostic factor. Recurrences are common (40–50%) and commonly develop within two years after treatment.[13,14] The prognosis is unfavorable, with survival rates as low as 58% in 2 years and 25% in 5 years.[12,14,17] Bone invasion, surgical margins, perineural and perivascular invasion, extracapsular spread, and histological grade, are predictors of loco-regional recurrence and a low survival rate.

HPV has been associated with some head and neck cancers, especially those of the oropharynx.[18,19,20] Importantly, there is an intriguing geographic disparity in the prevalence of HPV-positive head and neck cancers. The United States harbors a high prevalence (60%), Western Europe has moderate proportions (31%), and Brazil shows low indexes (4%) of HPV16-positive OP-SCC.[19] Since HPV-positive tumors have a better treatment response than HPV-negative ones, and a more favorable prognosis,[21,22] the last American Joint Committee on Cancer (AJCC) Staging Manual now classifies OP-SCC according to its HPV status, as assessed by p16 immunohistochemistry.[9,23]

The main goal of this study was to compare the survival rates of patients submitted to two different treatment modalities for advanced oropharynx carcinoma, namely surgery plus radiotherapy (Surg+RT) and chemotherapy plus radiotherapy (CT+RT). Another goal was to evaluate the effect of resectability on the survival rates.

Methodology

The study protocol was approved by the Research Ethics Committee of the Federal University of Minas Gerais (CAAE 54987815.1.0000.5149). The patients gave their written consent for participation in the study.

A cross-sectional observational study was performed according to STROBE guidelines. Medical files from the Head and Neck Surgery Department of the Hospital das Clínicas of the Federal University

of Minas Gerais (UFMG) (Brazil) were reviewed retrospectively from 2005 to 2015. The inclusion criteria comprised diagnosis of OP-SCC, no previous treatment, clinical TNM stage III and IV (AJCC 7th edition), and treatment performed at the Hospital das Clínicas UFMG. Patients with resectable tumors received Surg+RT, whereas those with unresectable tumors, or who refused the surgical approach were treated by CT+RT. The exclusion criteria were previously treated tumors, T1 and T2 tumors, under two-year follow-up period (as of the surgery or initial chemoradiotherapy date).

Information regarding the clinic and demographic features, and the response to treatment, were collected from the medical records. Variables included age, sex, smoking habit, alcohol intake, TNM staging, subsite, status at last follow-up, tumor resectability (criteria for unresectability: cervical N3 metastasis invading the common carotid artery or the skull base; primary tumor infiltrating the skull base and the internal carotid artery; involvement of the prevertebral fascia), and treatment modality.

The tumor samples (biopsy and/or surgical resection specimen) of the patients were retrieved from the files of the Laboratory of Pathologic Anatomy of the Hospital das Clínicas of UFMG and of the Hospital da Baleia. These samples were submitted to immunohistochemistry for p16 (CINtec® p16 Histology, ready-to-use, clone E6H4™, Roche, USA, code 06695230001). A sample of OP-SCC known to be p16-positive was included as the positive control. Negative control was obtained by omission of the primary antibody. The immunostaining was evaluated by two independent observers (A.M.L.S. and P.C.C.), according to criteria proposed by Lydiatt et al.[23] In brief, p16 overexpression was established when moderate to intense (+2/3) staining was seen diffusely (≥ 75%) in the tumor. Nuclear and cytoplasmic staining were considered when assessing the staining. Cytoplasmic coloration alone was considered unspecific. The cases were classified as positive or negative.

SPSS® version 19.0 and GraphPad Prism 7 software were used for the statistics. Descriptive analyses were performed. Pearson c^2 and Student's t-test were used to compare data regarding the clinical,

demographic and microscopic characteristics of the two treatment groups. Kaplan-Meier survival analysis was conducted, and the curves were compared by the log-rank test. P-values < 0.05 were considered significant.

Results

From 2005 to 2015, 75 patients were treated for advanced OP-SCC. Twenty-eight patients were excluded due to incomplete data on their medical records, rendering a final sample of 47 cases. Eighteen patients (38.3%) had resectable tumors and received Surg+RT for treatment. Twenty-nine (61.7%) individuals were treated with CT+RT (eighteen [62.1%] with unresectable tumors, and eleven [37.9%] patients who refused surgical treatment, despite having a resectable tumor).

Clinical and demographic data are presented in Table 1. All the variables shown in Table 1 were statistically similar between the two treatment groups (p > 0.05), except for N stage (p < 0.05). Middle-aged men, with smoking and drinking habits, composed the majority of the sample. Tumors were located mainly at the base of the tongue and were staged as T4N0 and TNM IV. Seventeen tumors were moderately differentiated and three were well differentiated. The remaining afforded no information regarding histological differentiation. Of the 23 cases made available for p16 testing, three (13.0%) tumors were positive. The other tumor samples could not be retrieved from the laboratory files, and were therefore not tested for p16. Two patients with p16+ tumors were non-smokers and non-drinkers, whereas the third case reported practicing these habits.

When comparing only the patients with resectable tumors, according to the treatment modality (Surg+RT vs. CT+RT), they presented similar clinical and demographic profiles (p > 0.05), except for the tumor subsite (p < 0.05) and the recurrence site (p = 0.055) (Table 1). Tumors of the base of the tongue and the lateral wall were more common in the Surg+RT group, whereas soft palate lesions were more frequent in the CT+RT group. Local or regional recurrence occurred only in the Surg+RT group.

Concerning the follow-up duration (mean 34.91 months) and response to treatment, 17 (36.2%) cases experienced recurrence. Sixteen (34.0%) patients remained alive without disease at the last follow-up, 15 (31.9%) died due to disease, and 9 (19.2%) were recurrent at the last follow-up (local, regional, or loco-regional) (Table 1).

Table 2 depicts the surgical treatment performed for the 18 patients treated with Surg+RT.

Survival analysis revealed similar overall and disease-free survival rates for patients treated with Surg+RT and CT+RT (p > 0.05, Figure A, B). Noteworthily, deaths in both groups occurred mostly at the beginning of the follow-up period, precisely during the first 24 months (Figure A). At this timepoint, 60.3% of CT+RT patients were expected to still be alive versus 80.79% of the Surg+RT group (Figure A). At the 5-year follow-up, 53.6% of the patients treated with CT+RT were expected to still be alive versus 73.3% of those submitted to Surg+RT (Figure A).

A similar overall picture was observed for the disease-free survival group. The early period (24 months into treatment) revealed a drastic drop in the curve, indicating 51.7% (CT+RT) and 70.6% (Surg+RT) of the patients without disease at this timepoint (Figure B). At the 5-year follow-up, 38.6% of the CT+RT and 45.8% of the Surg+RT patients were expected to be free of disease (Figure B).

Similar survival rates were noticed for the resectable tumors, comparing lesions treated by Surg+RT versus CT+RT (p>0.05, Figure C, D). Resectable tumors (grouping together those treated by Surg + RT and CT + RT) had overall survival rates similar to those of unresectable lesions (p > 0.05, Figure E), and a tendency toward better disease-free survival (p = 0.06, Figure F).

Considering that the soft palate lesion rates found in each treatment group were different, and that these lesions usually present a distinct growth pattern and response to treatment, we performed a complementary survival analysis excluding these lesions. The same was done for cN3 stage tumors, considering that the presence of N3 metastasis, per se, deteriorates a patient's prognosis. None of these complementary analyses revealed differences in

Table 1. Clinical and demographic information on 47 patients with advanced squamous cell carcinoma of the oropharynx, according to two different treatment protocols.

Variables	All patients (n = 47)	Surgery + RT (n=18)	CT+RT (n=29)			p-value [a]	
			Resectable, but refused surgery (n = 11)	Unresectable (n = 18)	Total (n = 29)	(all Surg+RT patients versus all CT+RT patients)	(all Surg+RT patients versus resectable tumors treated by CT+RT)
Age						0.964[b]	0.246[b]
Minimum	36	36	43	41	41		
Maximum	79	75	67	79	79		
Mean	56.3	56.22	52.45	58.72	56.34		
Sex						0.528	0.566
Female	6 (12.8)	3 (16.7)	1 (9.1)	2 (11.1)	3 (10.3)		
Male	41 (87.2)	15 (83.3)	10 (90.9)	16 (88.9)	26 (89.7)		
Smoking habit						0.306	N/A
Yes	40 (85.1)	14 (77.8)	10 (90.9)	16 (88.9)	26 (89.7)		
No	2 (4.3)	0	0	2 (11.1)	2 (6.9)		
Missing	5 (10.6)	4 (22.2)	1 (9.1)	0	1 (3.4)		
Alcohol intake						0.193	N/A
Yes	35 (74.5)	13 (72.2)	8 (72.7)	14 (77.8)	22 (75.9)		
No	3 (6.4)	0	0	3 (16.7)	3 (10.3)		
Missing	9 (19.1)	5 (27.8)	3 (27.3)	1 (5.6)	4 (13.8)		
cT stage						0.760	0.411
T3	17 (36.2)	7 (38.9)	6 (54.5)	4 (22.2)	10 (34.5)		
T4	30 (63.8)	11 (61.1)	5 (45.5)	14 (77.8)	19 (65.5)		
cN stage						0.025*	0.569
N0	14 (29.8)	4 (22.2)	5 (45.5)	5 (27.8)	10 (34.5)		
N1	9 (19.1)	5 (27.8)	3 (27.3)	1 (5.6)	4 (13.8)		
N2	11 (23.4)	7 (38.9)	3 (27.3)	1 (5.6)	4 (13.8)		
N3	12 (25.5)	1 (5.6)	0	11 (61.1)	11 (37.9)		
Missing	1 (2.1)	1 (5.6)	0	0	0		
TNM clinical staging						0.391	0.331
III	10 (21.3)	5 (27.8)	5 (45.5)	0	5 (17.2)		
IV	37 (78.7)	13 (72.2)	6 (54.5)	18 (100)	24 (82.8)		
Subsite						0.182	0.027*
Tonsil	13 (27.6)	3 (16.7)	4 (36.4)	6 (33.3)	10 (34.5)		
Base of tongue	17 (36.2)	9 (50.0)	1 (9.1)	7 (38.9)	8 (27.6)		
Soft palate	8 (17.0)	1 (5.6)	5 (45.5)	2 (11.1)	7 (24.1)		
Posterior wall	2 (4.3)	1 (5.6)	0	1 (5.6)	1 (3.4)		
Lateral wall (tonsil pillars)	7 (14.9)	4 (22.2)	1 (9.1)	2 (11.1)	3 (10.3)		
Recurrence						0.760	0.523
Yes	17 (36.2)	7 (38.9)	3 (27.3)	7 (38.9)	10 (34.5)		
No	30 (63.8)	11 (61.1)	8 (72.7)	11 (61.1)	19 (65.5)		

Continue

Continuation

Site of recurrence						0.119	0.055
Local	5 (29.4)	3 (42.9)	0	2 (11.1)	2 (20.0)		
Regional	4 (23.5)	3 (42.9)	0	1 (5.6)	1 (10.0)		
Loco-regional	4 (23.5)	0	2 (66.7)	2 (11.1)	4 (40.0)		
Distant	4 (23.5)	1 (14.3)	1 (33.3)	2 (11.1)	3 (30.0)		
Salvage (n=17)						0.809	N/A
Yes	2 (11.8)	1 (14.1)	0	1 (14.3)	1 (10.0)		
No	5 (29.4)	3 (42.9)	0	2 (28.6)	2 (20.0)		
Missing	10 (58.8)	3 (42.9)	3 (100)	4 (57.1)	7 (70.0)		
Follow-up (months)						0.178[b]	0.759[b]
Minimum	1	4	2	1	1		
Maximum	112	112	91	76	91		
Mean	34.91	42.28	38.55	25.33	30.34		
Status at last follow-up						0.422	0.611
Alive without disease	16 (34.0)	6 (33.3)	5 (45.5)	5 (27.8)	10 (34.5)		
Local recurrence	3 (6.4)	1 (5.6)	0	2 (11.1)	2 (6.9)		
Regional recurrence	2 (4.3)	2 (11.1)	0	0	0		
Loco-regional recurrence	4 (8.5)	2 (11.1)	0	2 (11.1)	2 (6.9)		
Distant metastasis	4 (8.5)	2 (11.1)	1 (9.1)	1 (5.6)	2 (6.9)		
Death (disease-related)	15 (31.9)	3 (16.7)	4 (36.4)	8 (44.4)	12 (41.4)		
Death (other causes)	2 (4.3)	1 (5.6)	1 (9.1)	0	1 (3.4)		
Missing	1 (2.1)	1 (5.6)	0	0	0		
p16						0.484	0.551
Positive	3 (6.4)	1 (5.6)	0	2 (11.1)	2 (6.9)		
Negative	20 (42.6)	11 (61.1)	4 (36.4)	5 (27.8)	9 (31.0)		
Not performed [c]	24 (51.1)	6 (33.3)	7 (63.6)	11 (61.1)	18 (62.1)		

RT: radiotherapy; CT: chemotherapy; Number in parenthesis represents percentages; N/A: statistics not performed because comparison group was null; [a]Pearson x^2; [b]Student T test; [c]Specimen not available for immunohistochemical testing. *statistically significant (<0.05).

survival rates (overall and disease-free) between the two treatment modalities (p > 0.05, data not shown).

Discussion

The current study revealed similar overall and disease-specific survival rates of patients with advanced OP-SCC treated with Surg+RT, compared with CT+RT. An unfavorable clinical outcome was evidenced irrespective of treatment modality, with 34.0% patients alive without disease at the last follow-up. Importantly, similar survival rates were seen when cN3 disease and p16+ tumors were included (13.0% prevalence in this study). The tendency toward a better disease-free survival rate observed for resectable tumors (grouping together those treated by Surg+RT and CT+RT) might be influenced by the higher volume of local and nodal disease present in the unresectable tumors, a scenario that represents a lower chance of disease control by chemoradiation. Accordingly, when analyzing only the resectable tumor group, there was no difference in the survival rates.

Taken together, the results are supportive of both modalities, Surg+RT and CT+RT, as being equally efficient in treating advanced OP-SCC. Therefore,

Table 2. Surgical approach for patients treated with surgery and radiotherapy (n = 18)

Variables	Absolute number (%)	p-value (Pearson x^2)
Type of surgery		0.135
Base Glossectomy + total laryngectomy	1 (5.6)	
Total Glossectomy + total laryngectomy	3 (16.7)	
Pelveglossomandibulectomy	6 (33.3)	
Transoral resection	1 (5.6)	
Base glossectomy	4 (22.2)	
Palatectomy	1 (5.6)	
Pharyngectomy	1 (5.6)	
Missing	1 (5.6)	
Neck dissection		0.002*
None	1 (5.6)	
Radical bilateral	5 (27.8)	
Radical unilateral	1 (5.6)	
Jugular bilateral	1 (5.6)	
Radical + jugular	10 (55.6)	
Surgical margin		0.003*
Negative (free)	14 (77.8)	
Positive	2 (11.1)	
Missing	2 (11.1)	

*Statistically significant. All patients also received radiotherapy.

morbidity and functional sequelae should be taken into account when choosing the best treatment modality for a given patient, individually. Whereas Surg+RT carries the morbidity of partial resection of organs involved in speaking and swallowing, CT+RT is usually associated with malnutrition, dysphagia and risk of aspiration. These variables (morbidity and sequelae) were not taken into account in the current research.

In the last update (8th Edition) of the AJCC guidelines, high-risk HPV-related oropharynx cancer was recognized as a unique disease, which usually affects young, non-smoking, non-drinking individuals, and presents an excellent response to treatment and good prognosis.[9] Therefore, the immunohistochemical overexpression of p16 was adopted as a biomarker for HPV-related carcinogenesis.[23] We found three p16-positive cases (13.0%), corroborating the low prevalence (4.1% to 14.3%) of HPV-related OP-SCC reported

in Brazil.[19,24,25,26] Importantly, only one of the three patients with p16+ tumors was a smoker and drinker. This patient had a worse clinical outcome (distant metastasis), whereas the other two (non-smokers and non-drinkers) remained alive without disease at the last follow-up. Accordingly, the results and interpretations of the survival analysis related herein mostly regard "conventional" OP-SCC, associated with tobacco and alcohol consumption. Finally, an interesting though specifically related observation was that the three p16-positive cases occurred in the tonsils and base of tongue, and the predilection of HPV-driven OP-SCC in the tonsils has already been addressed in the literature.[20]

HPV status has a strong influence on OP-SCC prognosis, and will probably drive treatment modality selection in the future. To date, modifying the treatment modality according to HPV status is still controversial, and should be undertaken only in clinical trials.[27,28] For this reason, OP-SCC
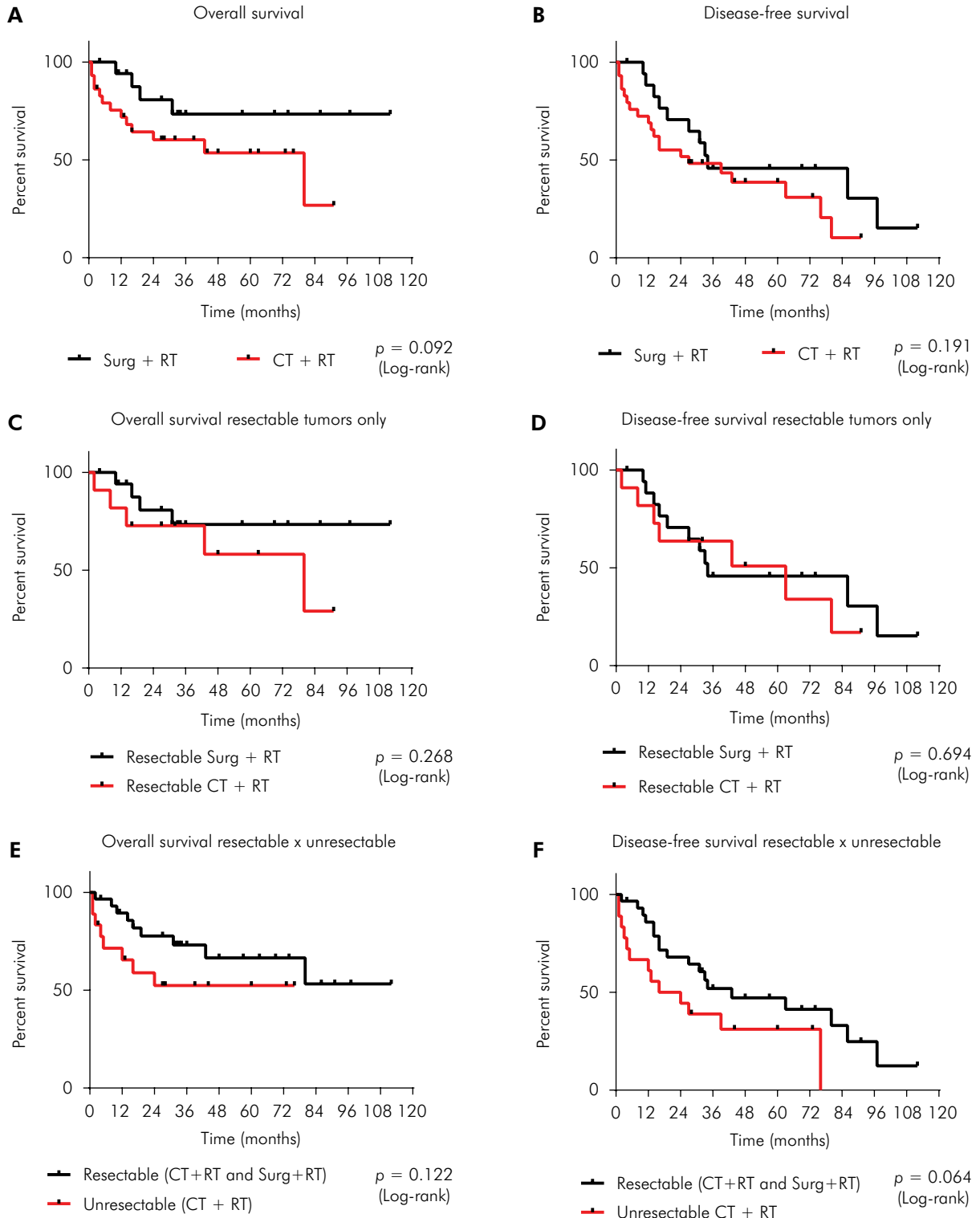
Figure. A, B: patients treated with surgery + radiotherapy (Surg+RT) had overall and disease-free survival rates similar to those treated by chemoradiotherapy (CT+RT) (p>0.05). C, D: Similar overall and disease-free survival rates were noticed for resectable tumors, comparing lesions treated by Surg+RT versus CT+RT (p>0.05). E, F: Resectable tumors (treated by Surg+RT and CT+RT, grouped together) presented similar overall survival rates with unresectable lesions (p > 0.05), and a tendency toward better disease-free survival rates (p = 0.06).

is often treated with chemoradiation, although radiation and cetuximab may also be used in some cases. The effect of combining radiation with both chemotherapy and cetuximab is also being studied. Any lesion that remains after chemoradiation is removed with surgery. If the cancer has spread to neck lymph nodes, it may also have to be removed (by lymph node dissection) after chemoradiation. Another option is to surgically remove cancer and neck lymph nodes first. This is often followed by radiation or chemoradiation to reduce the recurrence rates.[27,28] The treatment decision for individual patients will depend on the size, location and overall functional deficit of the tumor, as well as on patient preference and local expertise.

In our sample, relatively high percentages of patients were expected to be alive at the 5-year survival follow-up (53.6% and 73.3%, respectively). On the other hand, a high recurrence rate was noticed at the 5-year survival follow-up (38.6% and 45.8%). Recurrences and deaths are considered important factors during the first two years of follow-up, especially for patients not treated with surgery, thus reinforcing the importance of strict surveillance after treatment. Lastly, most patients were smokers and drinkers, thus stressing that the association of oropharynx cancer with such deleterious social habits urges wide-ranging community health efforts to promote educational and preventive actions.[20]

Conclusion

In conclusion, the two treatment protocols, namely surgery + radiotherapy and chemotherapy + radiotherapy, were equally efficient in treating advanced oropharynx squamous cell carcinoma, considering that both promoted similar overall and disease-free survival rates. Therefore, the decision regarding each treatment modality should be taken on a case-by-case basis, assessing the patient's overall clinical picture for tolerating the protocol, the sequelae of each treatment, and the patient's expectations. The results and interpretations of the survival analysis related herein mostly regard the diagnosis of "conventional" OP-SCC, since p16+ tumors were very uncommon in the current sample.

Acknowledgements

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