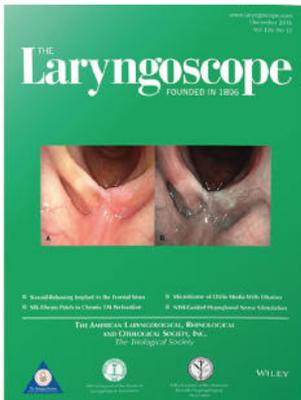




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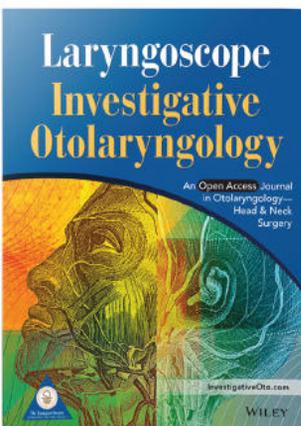


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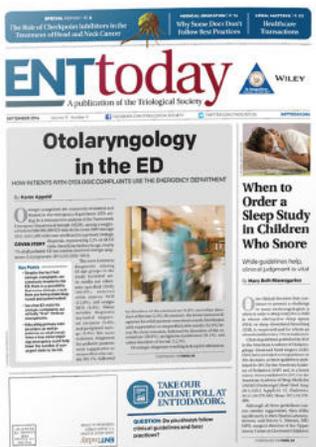
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## Effect of Postoperative Radiotherapy in pT1pN1cM0 and pT2p/cN0cM0 Oropharyngeal Squamous Cell Carcinoma

Lorenz Kadletz, MD ; Gregor Heiduschka, MD; Axel Wolf, MD; Anna Haug-Lettenbichler, MD; Lukas Poyntner, MD; Thomas Primosch, MD; Hermann Rogatsch, MD; Michael Formanek, MD; Matthias Stadler, MD; Lukas Kenner, MD, PhD; Hans E. Eckel, MD; Markus Brunner, MD 

**Objectives/Hypothesis:** Consulting of patients with oropharyngeal carcinoma, classified as pT1pN1cM0 and pT2p/cN0cM0, about postoperative radiotherapy is a precarious task as data are lacking. The aim of this study was to evaluate the effects of postoperative radiotherapy for patients with intermediate-stage oropharyngeal carcinoma.

**Study Design:** Multicentric retrospective study.

**Methods:** This analysis was conducted at seven Austrian institutions and included data of patients treated between 2000 and 2012. A total of 81 patients with oropharyngeal squamous cell carcinoma were included, of whom 33 patients received postoperative radiotherapy. p16 status determined by immunohistochemistry was available in 68 patients.

**Results:** Median follow-up was 47.9 months. Postoperative radiotherapy showed no benefits in regard to overall survival ( $P = .701$ ). In contrast, disease-free survival was significantly shortened in all patients without postoperative radiotherapy ( $P = .001$ ). When dividing the cohort in dependence of p16, p16-positive patients did not benefit from postoperative radiotherapy regarding overall and disease-free survival ( $P = .934$  and  $P = .102$ ), whereas p16-negative patients showed improved disease-free survival after postoperative radiotherapy ( $P = .007$ ). Multivariate analysis showed that outcome of postoperative radiotherapy is dependent on p16 status.

**Conclusions:** In terms of disease-free survival, patients with p16-negative tumors may benefit from postoperative radiotherapy, whereas survival of p16-positive patients is good regardless of additional treatment.

**Key Words:** Oropharyngeal carcinoma, T1N1, T2N0, adjuvant radiotherapy, postoperative radiotherapy, survival.

**Level of Evidence:** 4.

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### INTRODUCTION

Currently, global cancer statistics report escalating incidences of patients with oropharyngeal squamous cell carcinoma (OPSCC).<sup>1</sup> In the period between the years 2000 and 2012, over 40,000 patients were diagnosed with

OPSCC in the United States.<sup>2</sup> Infection with the human papillomavirus (HPV) is made primarily responsible for the rising numbers of OPSCC patients.<sup>3</sup> p16 expression is increasingly acknowledged as a surrogate marker for HPV infection.<sup>4,5</sup> Recent studies described concordance of high-risk HPV DNA status assessed by polymerase chain reaction and p16 staining in 92% to 93.4% of cases.<sup>6,7</sup>

To date, patients with early-stage OPSCC can be treated with either radiotherapy or surgery. Surgical resection without adjuvant therapy is an effective treatment for early-stage OPSCC.<sup>8,9</sup> The American College of Radiology (ACR) Appropriateness Criteria propose either surgery or definitive radiation for T1-2N0M0 resectable lateral OPSCC.<sup>10</sup> Adjuvant radiotherapy is usually necessary in patients with either lymph node metastases ( $N \geq 1$ ) or with large primary tumors ( $T \geq 3$ ), because this treatment concept is associated with increased survival rates and improved locoregional control.<sup>11,12</sup> According to the ACR Appropriateness Criteria, any OPSCC patient, regardless of the HPV status (T1-T2N1-2a M0), should receive definitive radiation alone, concurrent radio- and chemotherapy, or resection with neck dissection and adjuvant therapy.<sup>10</sup>

Radiotherapy in the head and neck region is often associated with substantial side effects.<sup>13</sup> In addition, full-dose reirradiation may influence disease-free survival. In cases of recurrent disease there is no benefit for

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overall survival (OS) rates.<sup>14,15</sup> Thus, the decision for adjuvant radiotherapy has to be carefully made considering side effects, the potential scenario of recurrent disease, and the limited effects of reirradiation on OS rates. However, data about the role of adjuvant radiotherapy for patients with intermediate-stage OPSCC, such as T1N1M0 and T2N0M0 classified patients, are very limited because of their relative scarcity. Hence, making clear recommendations regarding adjuvant radiotherapy can often be very challenging. Undeniably, adjuvant radiotherapy has consequences for patients in their further course of disease.

We therefore wanted to investigate the role of adjuvant radiotherapy in patients with T1N1M0 and T2N0M0 OPSCC. The purpose of this study was to investigate the rates of OS and recurrence-free survival (RFS) after surgical resection with or without adjuvant therapy.

## MATERIALS AND METHODS

### *Study Design and Patients*

This retrospective analysis was performed in three tertiary and four secondary hospitals in Austria. Patients with carcinomas of the oropharynx were investigated for eligibility. All patients (aged 18–90 years) with histologically verified squamous cell carcinomas of the oropharynx that were classified as pT1pN1cM0 or pT2p/cN0cM0 were enrolled in this study. T classification was always assessed as pathological classification. N stage was classified as either pN after neck dissection or cN without neck dissection. To create a uniform group of patients, stringent exclusion criteria were applied. Only patients with a primary diagnosis of OPSCC who were treated with transoral surgery in the period between the years 2000 and 2012 were included. Moreover, we determined whether postoperative radiotherapy was applied. We have included patients who were either treated with conventional three-dimensional conformal radiotherapy, intensity-modulated radiation therapy, or volumetric-modulated arc therapy. By means of histological reports, the resection margin status was assessed (R0, microscopically free margin; R1, cancerous cells seen microscopically at the margin; R2, macroscopic infiltration of the margin). Only patients with R0 status were included. In case of T1N1M0 OPSCC patients, the lymph node metastasis was evaluated for extracapsular spread (ECS) and excluded in cases of present ECS. Concomitant chemotherapy during adjuvant radiotherapy was seen as an exclusion criterion as well. Exclusion criteria also included definitive radiotherapy or concurrent chemoradiation as the primary treatment, recurrent disease, and a known secondary malignant disease. Moreover, patients with insufficient medical reports were excluded from further analysis. Institutional research board (IRB) approval was obtained prior to analysis. The IRB of the Medical University of Vienna served as a head committee (EK1052/2016).

### *Clinical Data*

Operative reports of all patients who were eligible for further analysis were investigated for the localization of the primary tumor (tonsils, base of the tongue, soft palate, and lateral oropharyngeal wall). Immunohistochemical staining of p16 was utilized as a surrogate parameter for HPV infection. If p16 was missing and the specimen was still available, immunohistochemical p16 staining was performed prospectively by the

respective pathology department. When p16 immunohistochemistry was performed, it was done using the Bench Mark Ultra platform (Ventana Medical Systems, Tucson, AZ). Slides were incubated with the primary antibody (p16-e6H4) and then evaluated by a pathologist.

Additionally, we analyzed if adjuvant radiotherapy and potential concurrent chemotherapy was applied. Only patients with postoperative radiotherapy alone with a maximum dose of 60 Gy were included in the analysis. All patients with concomitant chemotherapy or full-dose radiotherapy were excluded from this study. Medical reports were surveyed for the last date of follow-up. To calculate survival rates, the date of death and occurrence of recurrent disease were assessed in the event.

### *Statistical Methods*

Cumulative rates of OS and RFS were calculated by means of the Kaplan-Meier method. Statistical differences between groups were compared using the log-rank test (Mantel-Cox), and hazard ratios were calculated. Cox regression analysis was used for univariate and multivariate comparison. Variables with a  $P < .2$  were included for multivariate analysis. Moreover, descriptive statistics were used to describe the results. In addition, a Fisher exact test was used for comparison of categorical data between two groups. A  $\chi^2$  test was used in cases of three or more groups. Numerical variables such as age were compared with an independent  $t$  test.

SPSS software (version 23.0; IBM, Armonk, NY) and GraphPad Prism software (GraphPad Software, Inc., La Jolla, CA) were used to analyze and visualize data.

## RESULTS

### *Patients' Characteristics and Clinical Data*

A total of 81 patients met the inclusion criteria for this retrospective study (Fig. 1). The median age of investigated patients at the time of diagnosis was 59.0 years (range = 35.1–82.8 years; mean = 58.7 years). Median follow-up was 47.9 months (range = 2.1–92.2 months; mean = 49.8 months). The majority of our patients were male ( $n = 52$ , 64.2%). pT1pN1cM0 OPSCC was diagnosed in 31 patients and pT2p/cN0M0 in 50 patients. All patients with a pT1 tumor underwent neck dissection; therefore, N classification was always defined as pN1. Forty patients with a pT2 tumor underwent neck dissection, and 10 patients did not undergo surgery of the cervical lymph nodes; N classification was defined in 40 cases as pN0 and in 10 cases as cN0. In total, neck dissection was performed in 71 cases. Furthermore, we assessed the localization of the primary tumor. A total of 17 (20.9%) patients presented with a tumor in the base of the tongue, and 22 patients (27.2%) had a tumor localized at the soft palate. The majority ( $n = 37$ , 45.7%) of patients showed a primary tumor of the tonsils. Five patients (6.2%) had an OPSCC of the pharyngeal walls. Adjuvant radiotherapy was applied in 33 patients (40.7%). Median radiation dose was 60 Gy (range = 50–60 Gy). Because patients with risk factors were excluded, no patient obtained a higher radiation dosage than 60 Gy. It was possible to determine p16 in 68 patients of our cohort, out of whom 35 (51%) were positive for p16. A p16 status was already available in 33 patients and prospectively tested in 35 cases. We could

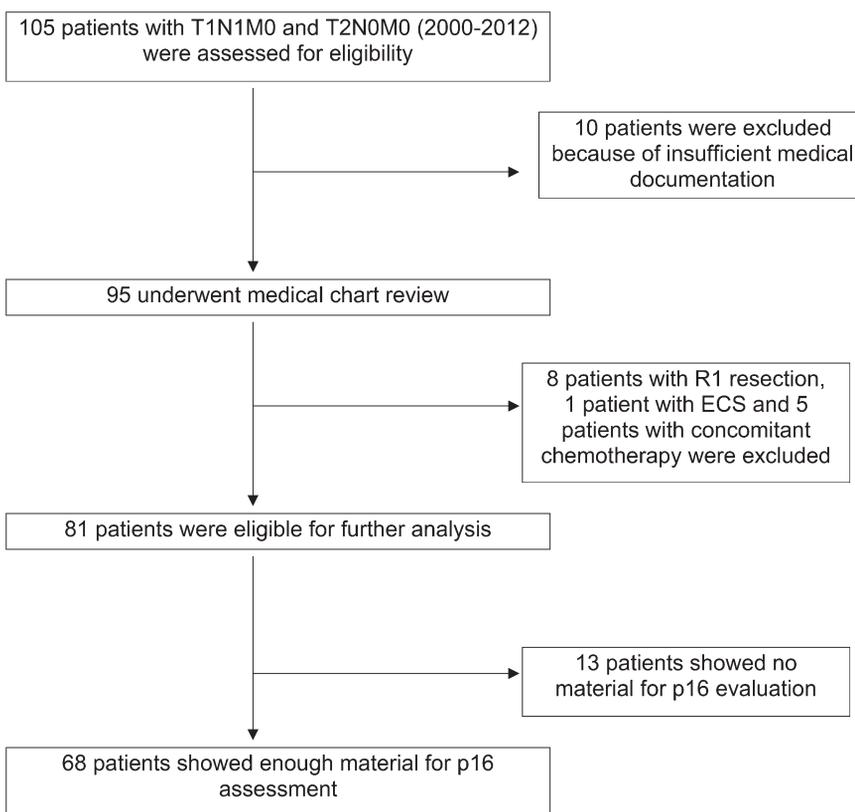


Fig. 1. Flowchart summarizing the enrollment of subjects for this study. ECS = extracapsular spread; R1 = cancerous cells seen microscopically at the margin.

not define p16 in 13 patients due to lacking histologic samples. Clinical data are shown in Table I.

### Effects of Adjuvant Radiotherapy on Survival

We wanted to analyze the effects of adjuvant radiotherapy on clinical outcome. First, patients with surgery alone were compared to patients who received adjuvant radiotherapy (Fig. 2, Table II). RFS was significantly shorter after surgical resection alone than after surgery plus adjuvant radiotherapy (hazard ratio [HR] for recurrence: 6.09, 95% confidence interval [CI]: 2.41-15.38,  $P = .001$ ). However, OS did not differ statistically between both groups (HR: 1.67, 95% CI: 0.50-5.62,  $P = .701$ ). A total of 18 recurrences (37.5%) occurred, and eight patients died (16.7%) after surgery alone. In contrast, a single patient (3.0%) developed recurrent disease, and three patients (9.1%) died when postoperative radiotherapy was applied. In cases of recurrent disease after surgery alone, 10 patients presented with local recurrence and six patients developed disease in the neck alone over time. In one patient, recurrent disease was detected locally as well as regionally. One patient developed both regional and distant metastases after initial treatment. Most interestingly, after adjuvant radiotherapy, no local or regional recurrence was detected. However, a single patient developed distant metastases after treatment. We did not assess any form of salvage treatment in cases of recurrent disease after initial therapeutic intervention.

We examined whether this effect of adjuvant radiotherapy applied to both of the TNM classifications we investigated (Fig. 3). Both evaluated classifications showed a significantly shorter RFS after surgical resection alone (T1N1M0 HR for recurrence: 7.39, 95% CI: 1.49-36.81,  $P = .015$  and T2N0M0 HR for recurrence: 4.35, 95% CI: 1.32-14.31,  $P = .016$ ). OS did not statistically differ in accordance to TNM classification (pT1pN1cM0  $P = .301$  and pT2p/cN0cM  $P = .579$ ).

Because HPV infection and p16 status are highly influencing factors on outcome in OPSCC patients, we compiled survival data according to p16 status (Fig. 4). Interestingly, the survival of p16-positive patients did not improve with postoperative radiotherapy, as almost all patients survived regardless of adjuvant treatment. In contrast, p16-negative OPSCC patients had significantly longer RFS (HR for recurrence: 5.44, 95% CI: 1.59-18.65,  $P = .007$ ) when postoperative radiotherapy was applied. Although p16-negative patients showed higher OS rates after 5 years (100% vs. 70.6%), a log-rank test could not reveal a statistically significant difference between both groups (HR for death: 3.737, 95% CI: 0.47-29.50,  $P = .211$ ).

Because our inclusion criteria were very strict, we analyzed both groups for statistically significant differences to rule out a selection bias (Table I). First, we compared all patients with surgical resection only to those who received postoperative radiotherapy. We could not detect any statistically significant difference between these two groups. However, patients without postoperative radiotherapy

TABLE I.  
Baseline Characteristics and Statistical Comparison of Patients With and Without Postoperative RT.

Total Cohort	Adjuvant RT, n = 33	No Adjuvant RT, n = 48	P Value
Age, yr, mean	60.04	57.66	.3365
Sex, male	23	29	.4817
TNM, pT1pN1cM0	15	16	.3529
Neck dissection	30	41	.5163
Subsite			
Base of the tongue	10	7	
Tonsil	16	21	
Soft palate	4	18	
Pharyngeal wall	3	2	.0502
p16 positive	15/24	20/44	.2113
Recurrences	1	18	.0025
Local	0	10	
Regional	0	6	
Distant	1	0	
Local + regional	0	1	
Regional + distant	0	1	
Death	3	8	.2593
p16 positive	Adjuvant RT, n = 15	No adjuvant RT, n = 20	
Age, yr, mean	61.23	59.98	.7463
Sex, male	12	10	.0891
TNM, pT1pN1cM0	6	8	>.9999
Neck dissection	15	19	>.9999
Subsite			.1328
Base of the tongue	6	4	
Tonsil	8	12	
Soft palate	0	4	
Pharyngeal wall	1	0	
Recurrences	0	3	.1167
Local	0	2	
Regional	0	1	
Distant	0	0	
Local + regional	0	0	
Regional + distant	0	0	
Death	1	1	.8335
p16 negative	Adjuvant RT, n = 9	No Adjuvant RT, n = 24	
Age, yr, mean	56.87	55.24	.7280
Sex, male	6	16	>.9999
TNM, pT1pN1cM0	5	5	.0895
Neck dissection	8	21	>.9999
Subsite			.0657
Base of the tongue	2	3	
Tonsil	5	7	
Soft palate	0	12	
Pharyngeal wall	2	2	
Recurrences	0	12	.0078
Local	0	8	
Regional	0	4	
Distant	0	0	
Local + regional	0	0	
Regional + distant	0	0	
Death	0	5	.1371

RT = radiotherapy.

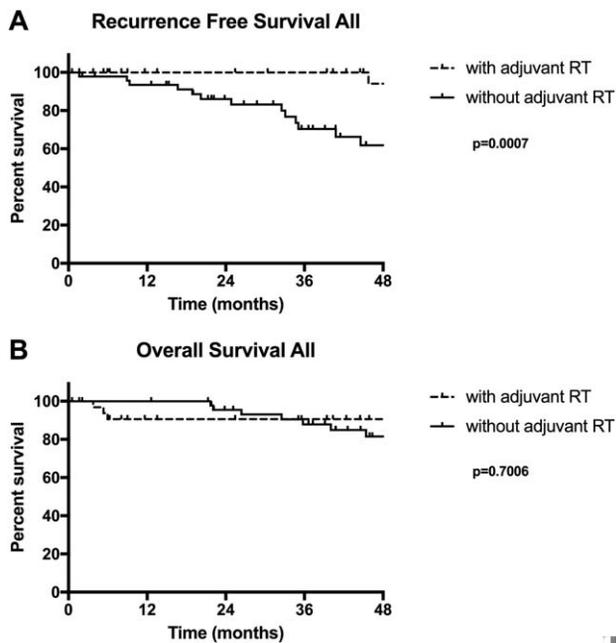


Fig. 2. Recurrence-free survival (A) and overall survival (B) for patients with intermediate-stage oropharyngeal carcinoma (pT1pN1M0 and pT2p/cN0M0) after either surgery alone or adjuvant RT. RT = radiotherapy.

showed a much higher rate (37.5%) of tumors located in the soft palate than those with adjuvant treatment (12.5%,  $P = .050$ ). Moreover, we stratified these two groups in p16-positive and negative patients. Again, statistical analyses showed no significant differences in dependence of the adjuvant treatment. Interestingly, in p16-positive patients, there were more male patients in the group with postoperative radiotherapy (80% vs. 50%,  $P = .089$ ). In p16-negative patients, the most striking difference occurred in the distribution of the primary tumor's localization. Here we observed a higher incidence of tumors localized in the soft palate in cases of no postoperative radiotherapy (50% vs. 0%,  $P = .066$ ).

We wanted to evaluate the independency of parameters and their significance on survival. As shown in Table III, only p16 and adjuvant radiotherapy had a significant effect on disease-free survival after univariate analysis ( $P = .004$  and  $.010$ , respectively). TNM stage, neck dissection, sex, and the localization did not influence survival significantly ( $P = .599$ ,  $P = .615$ ,  $P = .637$ , and  $P = .375$ , respectively). As expected, after analyzing these parameters in multivariate analysis, the results showed that the effect of adjuvant radiotherapy is totally depending on p16 status ( $P = .006$ ).

## DISCUSSION

In central Europe, there is a longstanding tradition of treating early-stage oropharyngeal cancer with transoral surgery. In advanced stages without additional risk factors, the operations are usually followed by a reduced dose (50–60 Gy) of radiotherapy.<sup>16</sup> In cases of R1 or R2 resection, ECS, or perineural invasion, full-

dose radiotherapy or concomitant chemoradiation can be applied.<sup>17–19</sup>

However, the role of adjuvant radiotherapy for patients with intermediate-stage OPSCC, classified as pT1pN1cM0 and pT2p/cN0cM0, has not been well defined yet, mainly due to insufficient data. To the best of our knowledge, this retrospective multicenter analysis is the first study that focuses on pT1pN1cM0 and pT2p/cN0cM0 OPSCC patients treated with surgical resection and adjuvant radiotherapy. To establish a homogeneous cohort we only included patients with squamous cell carcinoma of the oropharynx classified either pT1pN1cM0 or pT2p/cN0cM0. Because neck dissection was not performed in all cases of pT2 tumors, N classification was either pN0 or cN0. However, performing neck dissection in these cases did not seem to have an effect on outcome. We deliberately excluded patients with adverse features (R1 resection, ECS, and patients who for whatever reason received either full-dose radiotherapy or concomitant chemotherapy). Particular focus was set on p16 status, because both HPV and p16-negative patients are regarded as high-risk groups.<sup>20</sup> However, due to the multicentric design and the retrospective analysis, p16 status was not available in all cases.

Within our cohort we could demonstrate that patients with both pT1pN1cM0 and pT2p/cN0cM0

	Adjuvant RT	No Adjuvant RT	P Value
Total collective			
5-year RFS	94.1%	27.8%	.0007
HR (95% CI)		6.1 (2.4-15.4)	
5-year OS	90.6%	76.1%	.7006
HR (95% CI)		1.7 (0.5-5.6)	
T1N1M0			
5-year RFS	100%	44.9%	.0146
HR (95% CI)		7.4 (1.5-36.8)	
5-year OS	92.9%	100%	.3006
HR (95% CI)		0.12 (0.0; 6.4)	
T2N0M0			
5-year RFS	88.3%	35.3%	.0156
HR (95% CI)		4.4 (1.3-14.3)	
5-year OS	88.2%	64.3%	.5793
HR (95% CI)		2.0 (0.6-7.4)	
p16 positive			
5-year RFS	100%	72.2%	.1016
HR (95% CI)		6.8 (0.7-67.2)	
5-year OS	93.3%	88.9%	.9335
HR (95% CI)		0.8 (0.1-14.3)	
p16 negative			
5-year RFS	100%	24.7%	.0070
HR (95% CI)		5.4 (1.6-18.7)	
5-year OS	100%	70.6%	.2111
HR (95% CI)		3.7 (0.5-29.5)	

CI = confidence interval; HR = hazard ratio; OS = overall survival; RFS = recurrence-free survival; RT = radiotherapy.

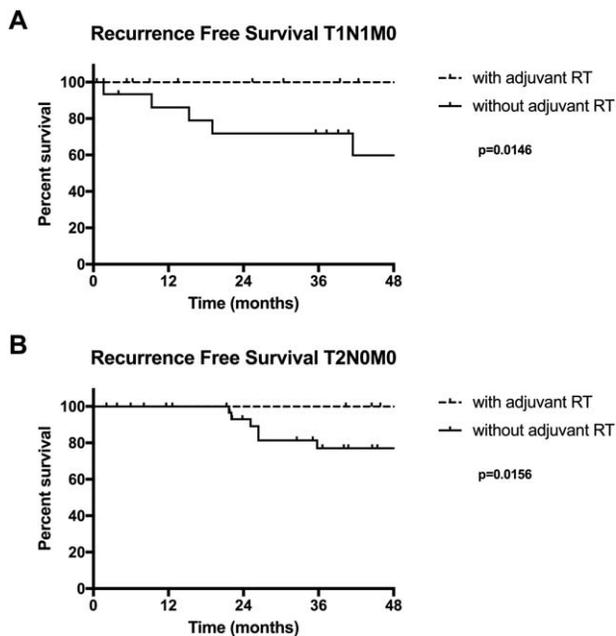


Fig. 3. Recurrence-free survival in dependence of the TNM classification. (A) Kaplan-Meier estimates of patients with pT1pN1cM0. (B) Patients classified as pT2p/cN0cM0. RT = radiotherapy.

showed significantly increased RFS survival rates with adjuvant radiotherapy. Further stratification by p16 status demonstrated that only p16-negative patients seemed to benefit from adjuvant radiotherapy, whereas basically all p16-positive patients survived without any signs of recurrent disease, regardless of adjuvant treatment. OS showed reduced survival proportions for p16-negative patients without adjuvant radiotherapy as well. However, these results remained statistically insignificant. It may be that

studies on larger sample sizes will reveal benefits in mean of OS. Current recommendations for treatment of T1-2N1-2aM0—either HPV positive or negative—OPSCC include definitive radiation alone, concurrent chemoradiation, or transoral surgery with neck dissection and appropriate adjuvant therapy.<sup>10</sup> Our results suggest that patients with p16-negative OPSCC should probably be treated with both, surgical resection and adjuvant radiotherapy. We tried to analyze the effects of adjuvant radiotherapy for pT1pN1cM0 OPSCC in accordance with p16 status as well. The sample size for this analysis was limited (n = 14 for p16 positive and n = 13 for p16 negative). However, no recurrence or death occurred in p16-positive patients and in the p16-negative patients treated with adjuvant radiation. Interestingly, it was possible to observe higher recurrence rates after surgery only in p16-negative patients (62.5% vs. 12.5%). It has to be mentioned that survival analysis showed no statistical significant difference.

ACR Appropriateness Criteria recommend either definitive radiation or definitive surgery for T1-2N0M0 OPSCC patients.<sup>10</sup> Our findings for pT2p/cN0M0 OPSCC are in contrast to these recommendations for p16-negative patients. In our cohort, it was possible to measure a significantly reduced RFS after surgical resection alone. Again, recurrent disease was most often detected in p16-negative patients without adjuvant radiotherapy. Our results showed that in cases of p16 negativity, adjuvant radiotherapy may be a highly recommended treatment option. Kass and colleagues investigated the oncologic outcome in early- and intermediate-stage OPSCC patients after surgery.<sup>8</sup> Their results showed that RFS of patients receiving adjuvant radiotherapy did not differ from patients treated with surgery alone, despite the higher risk profile of patients who were treated with adjuvant radiotherapy. In spite of an underpowered study population, they conclude that

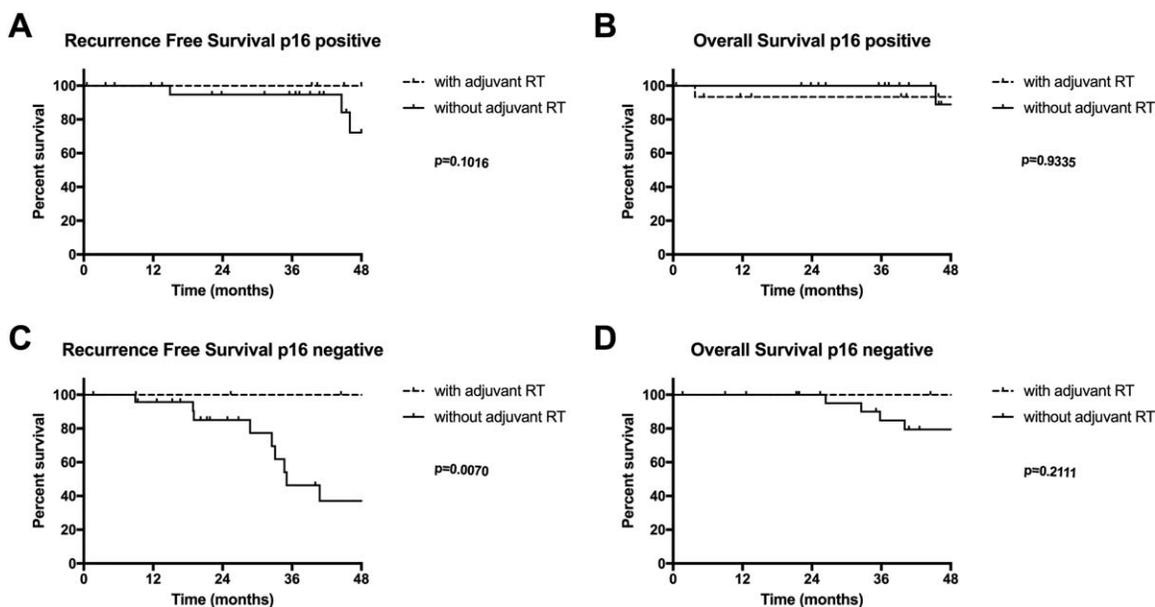


Fig. 4. Survival curves according to p16 expression. (A, B) Survival data of p16-positive patients. (C, D) Survival data of p16-negative patients. RT = radiotherapy.

TABLE III.  
Univariate and Multivariate Analysis of Disease-Free Survival.

	Univariate		Multivariate	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Adjuvant radiotherapy	0.3 (0.1-0.7)	.010	0.002 (0.0-1.8 × 10 <sup>76</sup> )	.945
p16 status	0.4 (0.2-0.7)	.004	0.4 (0.2-0.8)	.006
T1N1 vs. T2N0	0.8 (0.5-1.4)	.599		
Neck dissection	0.9 (0.5-1.6)	.615		
Sex, female	0.4 (0.3-2.0)	.637		
Localization		.375		
Base of the tongue	1.0			
Tonsil	0.3 (0.04-2.9)			
Soft palate	0.2 (0.03-1.9)			
Pharyngeal wall	0.6 (0.1-4.9)			

CI = confidence interval; HR = hazard ratio.

adjuvant radiotherapy may be useful for HPV-negative patients.

Our data strongly support the application of adjuvant radiotherapy in pT1pN1cM0 and pT2p/cN0cM0 p16-negative OPSCC patients. However, recent National Comprehensive Cancer Network guidelines state that there is still a lack of knowledge about the impacts of HPV infection, and it should not influence therapeutic decisions.<sup>21,22</sup> Our data support the current consensus that de-escalation of therapy in HPV/p16-positive patients may reduce treatment-associated comorbidities and long-term consequences with the same oncologic outcome. Several studies addressing de-intensification of chemotherapy in HPV-positive patients are being conducted (Radiation Therapy Oncology Group 1016, Tasman Radiation Oncology Group 12.01, DeESCALaTE [Determination of Epidermal growth factor receptor inhibitor (cetuximab) versus Standard Chemotherapy (cisplatin) early And Late Toxicity Events in Human Papillomavirus]). Moreover, some ongoing surgical studies investigate de-escalation after transoral surgery (Eastern Cooperative Oncology Group 3311, SiRS [The Sinai Robotic Surgery Trial in HPV Positive Oropharyngeal Squamous Cell Carcinoma], and ADEPT [Adjuvant De-escalation, Extracapsular Spread, P16+, Transoral Trial for Oropharynx Malignancy]).<sup>23</sup>

There are some limitations of our multicenter study. First, the retrospective character of the study limits the expressiveness of our results in comparison to prospective clinical trials. Due to the multicentric design, it was not possible to assess disease-specific survival. Additionally, sample sizes of the subgroups, such as p16-positive pT2p/cN0cM0, were not large enough to assess a statistically significant impact of these results.

## CONCLUSION

We were able to demonstrate that surgically treated p16-negative pT1pN1cM0 and pT2p/cN0cM0 patients with clear resections margins and without perineural invasion or extracapsular spread showed a significantly

better RFS with adjuvant radiotherapy compared to those treated with resection alone, whereas p16-positive patients do not seem to benefit from additional treatment.

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