European Archives of Oto-Rhino-Laryngology
https://doi.org/10.1007/s00405-026-10539-8

HEAD AND NECK

Influence of resection status on overall survival in p16-positive oropharyngeal carcinoma – a retrospective analysis of cancer registry data

Theodoros Kazopoulos[1] · Anne von Rüsten[2] · Constanze Schneider[2] · Stephan L. Schöbel[1] · Sonia Ziegler[3] · David Alexander Ziegler[3] · Michael Herzog[1]

Received: 22 May 2026 / Accepted: 28 July 2026

Abstract

Purpose HPV-associated oropharyngeal squamous cell carcinomas show better treatment response and survival than HPV-negative tumors. Immunohistochemical p16 expression is a validated surrogate for HPV association. While resection status (R0 vs. R1) is traditionally considered prognostic, its interaction with p16 status after primary surgery is unclear. This study evaluated the combined impact of p16 status and resection margins on overall survival.

Methods A retrospective analysis of the Berlin-Brandenburg cancer registry included patients with non-metastatic OPSCC treated between 2017 and 2023 by primary surgery followed by postoperative radiotherapy with or without systemic therapy. Patients were stratified into four groups: p16−/R0, p16−/R1, p16+/R0, and p16+/R1. Overall survival was assessed using Kaplan–Meier analysis and log-rank testing. Multivariable Cox regression adjusted for age, sex, pT/pN category, ECOG status, systemic therapy, and radiotherapy dose.

Results A total of 540 patients were included (p16−/R0: 142; p16−/R1: 19; p16+/R0: 325; p16+/R1: 54). Among R0 resections, p16-positive tumors showed significantly longer survival than p16-negative tumors (multivariate HR 0.26; $p<0.001$). A similar advantage for p16-positive vs. p16-negative tumors was observed in R1 resections (multivariate HR 0.35; $p=0.030$). Resection status (R1 vs. R0) was not significantly associated with survival in p16-negative (HR 0.86; $p=0.706$) or p16-positive tumors after multivariable adjustment (HR 1.74; $p=0.112$).

Conclusion p16 status was a stronger prognostic factor than resection margins. Overall survival did not differ significantly between R0 and R1 resection after multivariable adjustment. These results support further prospective testing into surgical de-escalation strategies. Just accepting an R1 margin would shift treatment burden towards intensified adjuvant therapy rather than reduce it.

Keywords Oropharynx carcinoma · HPV · P16 · Resection margins · Survival

Introduction

Squamous cell carcinomas of the oropharynx (OPSCC) are associated with human papillomavirus (HPV) infection in 15–70% of cases [1–5] and p16 is considered a surrogate marker for HPV association in OPSCC (p16 + OPSCC). Several publications demonstrate improved treatment response and overall survival for p16 + OPSCC compared to p16 − OPSCC, regardless of the treatment modalities used [1, 6–12].

Another key prognostic factor is the resection status of the primary tumor (R0 vs. R1). An R0 resection is considered a very strong prognostic marker for head and neck cancer

✉ Michael Herzog
m.herzog@mul-ct.de

1 Department of Otorhinolaryngology, Head and Neck Surgery, Medical University Lausitz – Carl Thiem, Cottbus, Germany

2 Clinical-Epidemiological Cancer Registry Brandenburg-Berlin, Berlin, Germany

3 Department of Radiation Oncology, Medical University Lausitz – Carl Thiem, Cottbus, Germany

Published online: 19 August 2026

[13–17]. Accordingly, an R0 resection is an important criterion to be achieved in the context of surgical planning.

With the implementation of the 8th edition of the TNM classification (TNM 8) in 2017 [18], HPV-associated OPSCC is classified as a separate entity. Since then, the surrogate marker p16 has been recorded in cancer registries worldwide for the documentation of OPSCC, allowing HPV-associated (p16+) and HPV-independent (p16-) OPSCC to be distinguished in tumor documentation. After several years of implementing p16 documentation, it is now possible to retrospectively access sufficiently large cohorts to not only compare groups of p16 + vs. p16 − OPSCC but also to draw conclusions about subgroups of p16+/p16 − OPSCC. Such a subgroup of OPSCC can be defined in terms of the resection status (R0 vs. R1) of p16+/p16 − OPSCC. It remains unclear how the two factors—p16 status and R status—interact to influence overall survival following primary surgical therapy for OPSCC.

The aim of the present study was to conduct a retrospective analysis of cancer registry data from patients with p16+/p16−classified OPSCC and R0 or R1 status following primary surgical therapy with subsequent (chemo)radiotherapy for the cancer, with regard to overall survival.

Methods

Definition of patient cohorts and hypotheses

The patients included in the analysis had squamous cell carcinoma of the oropharynx, underwent primary surgical treatment followed by postoperative treatment with radiation therapy ± systemic therapy, and were divided into four cohorts that were compared in terms of overall survival.

- p16−/R0
- p16−/R1
- p16+/R0
- p16+/R1

Given that patients with p16 + OPSCC demonstrate improved overall survival compared to p16 − OPSCC, and based on the assumption that an R0 resection status is a decisive prognostic marker for overall survival, the following hypotheses were defined for patients with OPSCC.

Hypothesis 1: p16+ / R0 shows better overall survival than p16− / R0

Hypothesis 2: p16+ / R1 shows better overall survival than p16− / R1

Hypothesis 3: p16− / R0 shows better overall survival than p16− / R1

Hypothesis 4: p16+ / R0 shows better overall survival than p16+ / R1

Data acquisition

A retrospective data collection was conducted from the Brandenburg-Berlin Clinical-Epidemiological Cancer Registry (KKRBB), with the data status 29 August 2025. A detailed breakdown by individual clinics could not be provided for data protection reasons. The KKRBB is responsible for documenting oncological data for approximately 6,191,000 individuals (population of Berlin and Brandenburg in 2021 according to www.destatis.de).

Cases diagnosed between January 1, 2017 (introduction of TNM 8 with documentation of p16 status) and December 31, 2023 (compliance with a minimum follow-up of 1 year) were included. The study included patients with squamous cell carcinoma of the oropharynx who were registered as residents of Brandenburg or Berlin at the time of diagnosis and for whom p16 status was available. Oropharyngeal carcinoma was defined based on the documented ICD-10 code (Version 18; carcinomas of the base of the tongue: C01; carcinomas of the lingual tonsil: C02.4; carcinomas of the palate: C05.1, C05.2, C05.8; tonsil carcinomas: C09.0, C09.1, C09.8, C09.9; oropharyngeal carcinomas: C10.0, C10.1, C10.2, C10.3, C10.4, C10.8, C10.9; malignant neoplasms of other parts of the pharynx: C14.2). An entity other than squamous cell carcinoma, a location outside the oropharynx as defined above, an unclear p16 status, an unknown resection status (Rx), or an R2 status and an M1 status were considered exclusion criteria. All included patients underwent local tumor resection as primary therapy, followed by postoperative therapy (radiation therapy ± chemo therapy). All included cases had to have a pathological T and N category. Given that patients with an R1 resection should always subsequently receive (chemo)radiotherapy, patients with an R0 resection without postoperative (chemo)radiotherapy were excluded in order to compare groups with identical treatment regimens and thereby rule out treatment-related bias.

Furthermore, the following were recorded: age at diagnosis, sex, ECOG-status at diagnosis, TNM, postoperative systemic therapy administered and the radiation dose (Gy) administered during postoperative therapy.

Study population

The study population included 3637 primary cases (Supplement 1).

After exclusion of histologies others than squamous cell carcinomas ($n = 225$), unknown p16-status ($n = 971$), no primary surgical therapy ($n = 1199$), unknown pT, pN, M1 after surgery ($n = 220$) and RX/R2-status ($n = 49$) a total of 973

OPSCC with primary surgical therapy and resection status R0/R1 were available.

The Patients were separated by the p16-status and patients with no postoperative radiotherapy were excluded.

A *Group OPSCC p16−*; $n=327$.

Excluded: no postoperative radiotherapy; $n=166$ (50.8%).
postoperative radiotherapy; $n=161$.

- Cohort OPSCC p16−/R0; $n=142$.
- Cohort OPSCC p16−/R1; $n=19$.

B *Group OPSCC p16+*; $n=646$.

Excluded: no postoperative radiotherapy; $n=267$ (41.3%).
postoperative radiotherapy; $n=379$.

- Cohort OPSCC p16+/R0; $n=325$.
- Cohort OPSCC p16+/R1; $n=54$.

The statistical analyses compare these four cohorts p16−/R0 ($n=142$), p16−/R1 ($n=19$), p16+/R0 ($n=325$), and p16+/R1 ($n=54$) with one another.

Statistical approach

For the aforementioned cohorts, Kaplan-Meier survival analysis and a group comparison using the log-rank test were performed. Survival time was calculated from the date of diagnosis to the date of death or to the cutoff date of December 31, 2024. The association between the R classification and overall survival was assessed using multivariate analysis (Cox regression). The following parameters were considered as covariates: age at diagnosis, sex, pathological T and N categories, ECOG status at diagnosis, administration of systemic therapy as postoperative therapy, and the radiation dose administered. The survival curves presented in the graph are based on confounder-adjusted as well as unadjusted calculations. The recurrence-free/progression-free survival time was calculated from the date of surgery to the date of recurrence or progression or to the cutoff date of December 31, 2023.

In the comparison of N classification between p16+OPSCC (maximum N2) and p16−OPSCC (maximum N3), N2 and N3 were combined into a single category for p16−OPSCC whenever necessary.

The UICC stage, which is derived from the TNM stages, is subject to downstaging for p16+OPSCC in TNM 8. Against this background, it does not make sense to define the UICC stage as a confounder, since p16+OPSCC would always have been classified lower than p16−OPSCC. The TNM classification appeared to be a more robust parameter for assessing the tumor situation.

Analyses were performed using R statistical software (Version 4.3.0, R Foundation for Statistical Computing, Vienna, Austria,).

Results

Effect of p16 status on overall survival following R0 resection in OPSCC

Age, Sex and pathological T-categories do not differ between the two cohorts (p16+/R0 ($n=325$), p16−/R0 ($n=142$)). The N-status differs between the two groups, with p16−OPSCC exhibiting a higher prevalence of advanced N-stages (p16+; N0: 28 (8.6%), N1: 225 (69.2%), N2-N3: 72 (22.2%)/p16−; N0: 26 (18.3%), N1: 24 (16.9%), N2-N3: 92 (64.8%); $p<0.001$). The ECOG status differs slightly ($p=0.049$) between both cohorts (p16+; ECOG 0: 167 (51.4%); ECOG 1: 40 (12.3%); ECOG 2–4: 7 (2.2%), no data: 111 (34.2%)/p16−; ECOG 0: 59 (41.5%); ECOG 1: 31 (21.8%); ECOG 2–4: 3 (2.1%)). Both cohorts did not differ in terms of received total dose of radiation ($p=0.284$; p16+; 61.3 Gy 95% CI [60.7–61.9]/p16−; 60.1 Gy 95% CI [60.7–61.9]/p16−; 60.1 [58.3–62.0]) and applied systemic therapy ($p=0.219$; p16+; 177 (54.5%)/p16−;73 (51.4%) (Supplement 1).

A higher T-stage as well as a higher N- stage has a stage-correlated negative impact on overall survival for both groups (Table 1). Patients with p16+OPSCC have improved overall survival compared to p16−OPSCC following R0 resection in both univariate and multivariate analyses, with a hazard ratio (HR) of 0.26 (95% CI 0.16–0.44, $p<0.001$) (Table 1; Fig. 1A, Supplement 1).

Hypothesis 1,"p16+ / R0 shows better overall survival than p16− / R0," can be confirmed based on these data.

Effect of p16 status on overall survival following R1 resection in OPSCC

Age, Sex, ECOG status and pathological T-categories do not differ between the p16+and p16−cohorts following R1 resection. Regarding N stages, p16+patients had a higher proportion of N1 stages (p16+; N0: 3 (5.6%), N1: 36 (66.7%), N2-N3: 15 (27.8%)/p16−; N0: 2 (10.5%), N1: 4 (21.1%), N2-N3: 13 (68.4%); $p=0.003$). (Supplement 1).

Table 1 Association of p16 status and other factors with overall survival in patients with OPSCC who underwent R0 tumor resection

Factor	Category	*N* (%)	HR (univariate)	HR (multivariate)
p16-status	negative	142 (30.4)	-	-
	positive	325 (69.6)	0.32 (0.21–0.46, $p<0.001$)	0.26 (0.16–0.44, $p<0.001$)
Age	Median [95% CI]	61.5 [60.6–62.6]	1.01 [0.99–1.03, $p=0.337$]	1.00 [0.97–1.02, $p=0.920$]
Sex	Female	93 (19.9)	-	-
	Male	374 (80.1)	1.04 (0.63–1.70, $p=0.890$)	0.81 (0.47–1.39, $p=0.436$)
Pathological T-category	T1	112 (24.0)	-	-
	T2	226 (48.4)	0.46 (0.27–0.78, $p=0.004$)	0.45 (0.25–0.79, $p=0.006$)
	T3	111 (23.8)	1.77 (1.10–2.85, $p=0.019$)	2.09 (1.25–3.50, $p=0.005$)
	T4	18 (3.9)	1.25 (0.48–3.23, $p=0.648$)	2.09 (0.71–6.16, $p=0.182$)
Pathological N-category	N0	54 (11.6)	-	-
	N1	249 (53.3)	1.54 (0.65–3.62, $p=0.327$)	4.38 (1.61–11.90, $p=0.004$)
	N2-N3 (N3 only in p16− carcinomas)	164 (35.1)	3.20 (1.37–7.43, $p=0.007$)	4.36 (1.69–11.26, $p=0.002$)
ECOG at diagnosis	ECOG 0	226 (48.4)	-	-
	ECOG 1	71 (15.2)	1.69 (1.03–2.77, $p=0.037$)	1.31 (0.76–2.27, $p=0.337$)
	ECOG 2–4	10 (2.1)	2.58 (0.93–7.18, $p=0.069$)	2.57 (0.91–7.29, $p=0.075$)
	unknown	160 (34.3)	0.80 (0.50–1.28, $p=0.358$)	0.81 (0.49–1.33, $p=0.402$)
Postoperative systemic therapy	yes	250 (53.5)	-	-
	no	217 (46.5)	0.96 (0.65–1.42, $p=0.850$)	1.41 (0.87–2.30, $p=0.164$)
Total dose of postoperative radiotherapy	Median [95% CI]	63.9 [63.9–63.9]	1.03 [0.99–1.07, $p=0.143$]	1.03 [0.99–1.07, $p=0.090$]

Comparison of overall survival between the p16+/R1 ($n=54$) and p16−/R1 ($n=19$) revealed a difference between the two groups (multivariate HR 0.35 (95% CI (0.13–0.90), $p=0.030$), with p16 status being the decisive factor for overall survival. (Table 2; Fig. 1B).

Hypothesis 2,"p16+ / R1 shows better overall survival than p16− / R1," can be confirmed based on these data.

Effect of R-status on overall survival in p16 – OPSSC

Patients with p16 − OPSCC and R1 status are more likely to have T3 and T4 stages (R0; T1: 32 (22.5%), T2: 61 (43.0%), T3: 42 (29.6%), T4: 7 (4.9%)/R1; T1: 2 (10.5%), T2: 5 (26.3%), T3: 7 (36.8%), T4: 5 (26.3%); $p=0.005$). There were no differences in N stages between the groups. Patients who underwent R1 resection received a higher total dose of postoperative radiation (R0 (mean [95% CI]); 60.1 [58.3–62.0]/R1 (mean [95% CI]); 65.2 [63.9–66.5]; $p=0.017$) and were more likely to receive additional systemic therapy (R0; 73 (51.4%)/R1; 15 (78.9%); $p=0.043$) The groups did not differ in terms of other characteristics (Age, Sex, ECOG). (Supplement 1).

An increasing N-stage correlates negatively with overall survival in patients with R0 and R1 status, as does an ECOG score > 1. Neither univariate nor multivariate analysis revealed a difference in overall survival between patients with p16−/R0 OPSCC and those with p16−/R1 OPSCC (multivariate HR 0.86 (95% CI 0.40–1.86), $p=0.706$) (Table 3; Fig. 1C).

Hypothesis 3,"p16− / R0 shows better overall survival than p16− / R1," cannot be confirmed based on these data.

Effect of R-status on overall survival in p16 + OPSCC

There is a difference in T-stages between patients who underwent R0 and R1 resection. Patients with R1 status had a higher incidence of T3 and T4 stages (R0; T1: 80 (24.6%), T2: 165 (50.8%), T3: 69 (21.2%), T4: 11 (3.4%)/R1; T1: 4 (7.4%), T2: 23 (42.6%), T3: 21 (38.9%), T4: 6 (11.1%); $p<0.001$). The N stages did not differ between the groups. Patients with R1 status were more frequently treated with systemic therapy in addition to postoperative radiation compared to patients with R0 status (R0; 177 (54.5%)/R1; 42 (77.8%); $p=0.002$. The radiation dose administered was higher in the R1 group (R0 (mean [95% CI]); 61.3 [60.7–61.9]/R1 (mean [95% CI]); 64.0 [61.9–66.2]; $p<0.001$) The

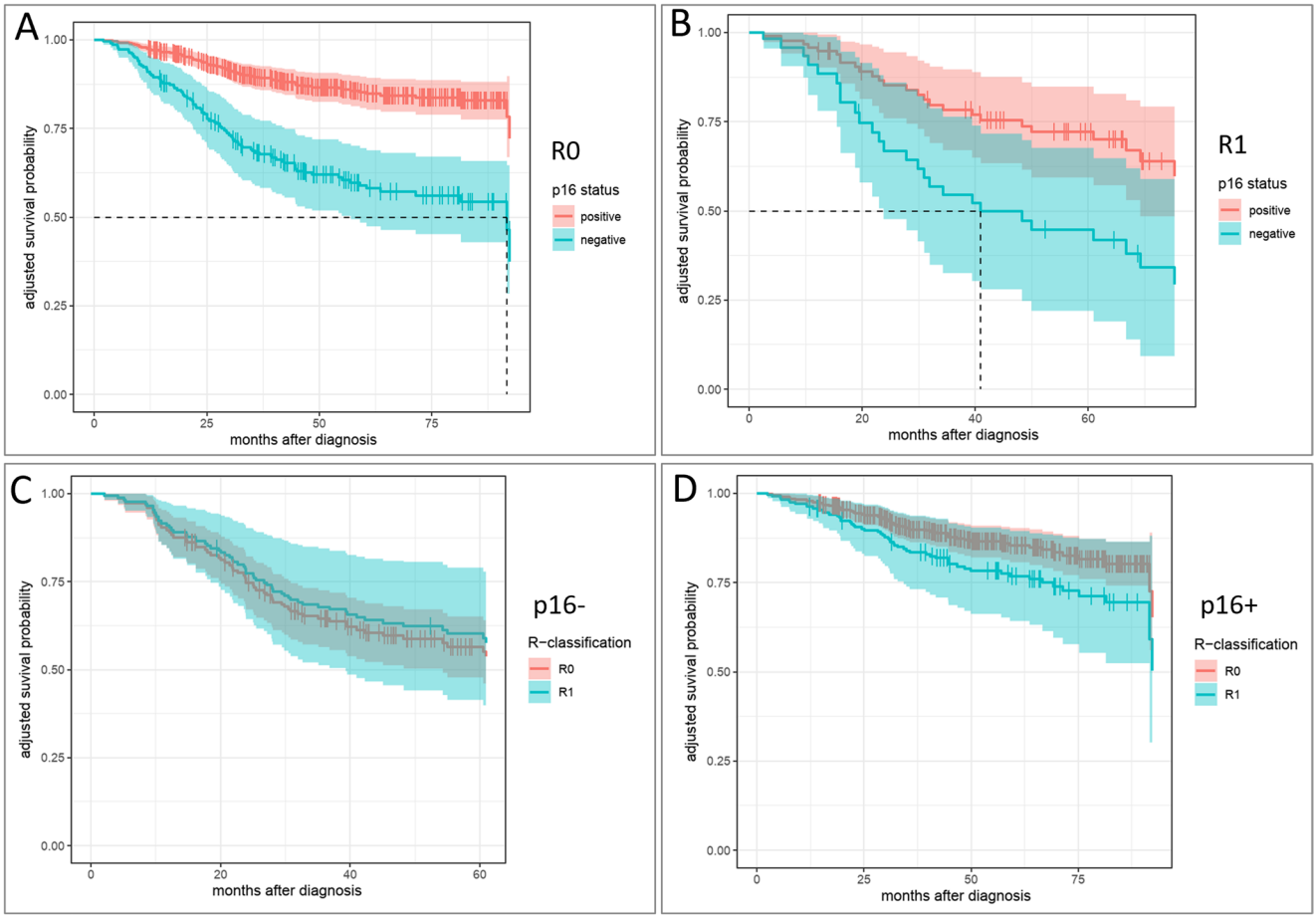

Fig. 1 **A-D**: Confounder-adjusted survival curves for the 4 cohorts compared. (**A**) Cohort p16+/R0 vs. p16−/R0. (**B**) Cohort p16+/R1 vs. p16−/R1. (**C**) Cohort p16−/R0 vs. p16−/R1. (**D**) Cohort p16+/R0 vs. p16+/R1. Adjustment for age, sex, pathological T and N category, ECOG performance status at diagnosis, postoperative systemic therapy as part of primary therapy, as well as total dose of radiotherapy

proportion of women was higher in the R1 group, in terms of other characteristics the groups did not differ (Age, ECOG). The abnormalities in the distribution of characteristics in R0 and R1 resected p16+carcinomas largely correspond to the abnormalities in p16- carcinomas (Supplement 1).

Higher T and N stages correlated negatively with overall survival in both groups.

Without adjustment for confounders, patients with an R1 resection had poorer overall survival than patients with an R0 resection (univariate HR 2.04 (95% CI 1.13–3.66), $p=0.017$). After adjustment - especially for the pathological T-category - no difference was observed between the groups (multivariate HR 1.74 (95% CI 0.88–3.46), $p=0.112$). In other words, the observed poorer survival rates can be attributed to the fact that patients who underwent R1 resection had more advanced T stages (Table 4; Fig. 1D).

Hypothesis 4,"p16+ / R0 shows better overall survival than p16+ / R1," cannot be confirmed based on these data.

Influence of the resection status on the recurrence-free/progression-free survival

R1 resection in patients with p16+OPSCC was associated with a significantly increased risk of recurrence or progression in the univariate model, but not after multivariate adjustment (HR univariate=2.31 (95% CI 1.12–4.76, $p=0.024$), HR multivariate=2.08 (95% CI 0.89–4.82, $p=0.089$) (Supplement 1).

Discussion

This study describes, for the first time, the overall survival of patients with p16+and p16−OPSCC stratified by the R-status in a larger cohort, based on a data collection from the Brandenburg-Berlin Clinical-Epidemiological Cancer Registry.

It is evident that patients with R0 status and p16 + OPSCC have better overall survival than patients with R0

Table 2 Association of p16 status and other factors with overall survival in patients with OPSCC who underwent R1 tumor resection

Factor	Category	*N* (%)	HR (univariate)	HR (multivariate)
p16-status	negative	19 (26.0)	-	-
	positive	54 (74.0)	0.39 (0.18–0.85, $p=0.019$)	0.35 (0.13–0.90, $p=0.030$)
Age	Median [95% CI]	62.3 [59.8–63.8]	1.02 [0.98–1.07, $p=0.370$]	1.02 [0.97–1.08, $p=0.408$]
Sex	Female	25 (34.2)	-	-
	Male	48 (65.8)	1.27 (0.55–2.92, $p=0.574$)	1.34 (0.47–3.83, $p=0.583$)
Pathological T-category	T1	6 (8.2)	-	-
	T2	28 (38.4)	2.20 (0.28–17.39, $p=0.455$)	4.21 (0.48–36.89, $p=0.194$)
	T3	28 (38.4)	2.40 (0.31–18.77, $p=0.405$)	4.21 (0.48–36.87, $p=0.194$)
	T4	11 (15.1)	3.71 (0.45–30.91, $p=0.225$)	7.66 (0.79–74.38, $p=0.079$)
Pathological N-category	N0	5 (6.8)	-	-
	N1	40 (54.8)	0.60 (0.13–2.72, $p=0.507$)	1.39 (0.23–8.44, $p=0.721$)
	N2-N3 (N3 only in p16 − carcinomas)	28 (38.4)	1.39 (0.31–6.20, $p=0.663$)	1.96 (0.33–11.63, $p=0.458$)
ECOG at diagnosis	ECOG 0	34 (46.6)	-	-
	ECOG 1	16 (21.9)	1.68 (0.67–4.19, $p=0.265$)	1.42 (0.48–4.18, $p=0.527$)
	ECOG 2–4	2 (2.7)	1.86 (0.24–14.55, $p=0.556$)	3.85 (0.41–36.43, $p=0.240$)
	unknown	21 (28.8)	0.87 (0.32–2.35, $p=0.783$)	0.94 (0.31–2.86, $p=0.918$)
Postoperative systemic therapy	yes	57 (78.1)	-	-
	no	16 (21.9)	0.72 (0.27–1.92, $p=0.515$)	0.47 (0.13–1.71, $p=0.254$)
Total dose of postoperative radiotherapy	Median [95% CI]	65.0 [63.9–65.6]	0.91 [0.85–0.97, $p=0.007$]	0.89 [0.82–0.97, $p=0.011$]

Table 3 Association of R status and other factors with overall survival in patients with p16 − OPSCC

Factor	Category	*N* (%)	HR (univariate)	HR (multivariate)
R-Classification	R0	142 (88.2)	-	-
	R1	19 (11.8)	1.55 (0.81–2.96, $p=0.186$)	0.86 (0.40–1.86, $p=0.706$)
Age	Median [95% CI]	61.9 [60.5–63.3]	1.02 [0.99–1.04, $p=0.241$]	1.00 [0.97–1.03, $p=0.856$]
Sex	Female	29 (18.0)	-	-
	Male	132 (82.0)	1.13 (0.60–2.11, $p=0.705$)	1.22 (0.58–2.53, $p=0.599$)
Pathological T-Category	T1	34 (21.1)	-	-
	T2	66 (41.0)	0.40 (0.21–0.79, $p=0.008$)	0.41 (0.20–0.86, $p=0.017$)
	T3	49 (30.4)	1.16 (0.63–2.13, $p=0.625$)	1.03 (0.50–2.13, $p=0.942$)
	T4	12 (7.5)	1.28 (0.56–2.96, $p=0.557$)	2.69 (0.90–8.10, $p=0.078$)
Pathological N-Category	N0	28 (17.4)	-	-
	N1	28 (17.4)	2.35 (0.95–5.82, $p=0.065$)	4.16 (1.48–11.69, $p=0.007$)
	N2	64 (39.8)	1.45 (0.62–3.37, $p=0.387$)	1.98 (0.73–5.32, $p=0.178$)
	N3	41 (25.5)	2.49 (1.06–5.82, $p=0.036$)	4.23 (1.49–11.99, $p=0.007$)
ECOG at diagnosis	ECOG 0	67 (41.6)	-	-
	ECOG 1	36 (22.4)	1.46 (0.82–2.62, $p=0.203$)	1.36 (0.71–2.61, $p=0.352$)
	ECOG 2–4	4 (2.5)	3.81 (1.15–12.61, $p=0.029$)	6.78 (1.79–25.58, $p=0.005$)
	unknown	54 (33.5)	0.68 (0.37–1.25, $p=0.216$)	0.85 (0.44–1.63, $p=0.617$)
Postoperative systemic therapy	yes	88 (54.7)	-	-
	no	73 (45.3)	0.76 (0.47–1.24, $p=0.277$)	1.40 (0.73–2.67, $p=0.307$)
Total dose of radiotherapy	Median [95% CI]	63.9 [63.9–64.0]	1.03 [0.99–1.07, $p=0.121$]	1.05 [1.00–1.10, $p=0.029$]

Table 4 Association of R status and other factors with overall survival in patients with p16 + OPSCC

Factor	Category	*N* (%)	HR (univariate)	HR (multivariate)
R-Classification	R0	325 (85.8)	-	-
	R1	54 (14.2)	2.04 (1.13–3.66, $p=0.017$)	1.74 (0.88–3.46, $p=0.112$)
Age	Median [95% CI]	61.4 [60.4–62.7]	1.01 (0.99–1.04, $p=0.334$)	0.99 (0.96–1.03, $p=0.741$)
Sex	Female	89 (23.5)	-	-
	Male	290 (76.5)	0.86 (0.48–1.54, $p=0.614$)	0.77 (0.41–1.43, $p=0.399$)
Pathological T-Category	T1	84 (22.2)	-	-
	T2	188 (49.6)	0.81 (0.40–1.66, $p=0.568$)	0.65 (0.30–1.40, $p=0.270$)
	T3	90 (23.7)	2.45 (1.24–4.86, $p=0.010$)	2.51 (1.19–5.31, $p=0.016$)
	T4	17 (4.5)	1.42 (0.40–5.04, $p=0.588$)	1.23 (0.32–4.81, $p=0.762$)
Pathological N-Category	N0	31 (8.2)	-	-
	N1	261 (68.9)	4.79 (0.66–34.88, $p=0.122$)	6.43 (0.86–48.03, $p=0.070$)
	N2	87 (23.0)	8.45 (1.14–62.76, $p=0.037$)	11.10 (1.46–84.48, $p=0.020$)
ECOG at diagnosis	ECOG 0	193 (50.9)	-	-
	ECOG 1	51 (13.5)	1.58 (0.82–3.04, $p=0.174$)	1.50 (0.71–3.16, $p=0.287$)
	ECOG 2–4	8 (2.1)	1.95 (0.46–8.15, $p=0.363$)	1.72 (0.40–7.38, $p=0.466$)
	unknown	127 (33.5)	0.86 (0.47–1.55, $p=0.612$)	1.03 (0.55–1.94, $p=0.931$)
Postoperative systemic therapy	yes	219 (57.8)	-	-
	no	160 (42.2)	0.94 (0.57–1.57, $p=0.822$)	1.12 (0.60–2.08, $p=0.717$)
Total dose of radiotherapy	Median [95% CI]	63.9 [63.9–63.9]	1.01 (0.96–1.07, $p=0.570$)	0.99 (0.95–1.04, $p=0.774$)

status and p16 − OPSCC. As expected, these results confirm existing studies that describe p16 + OPSCC as having a better prognosis compared to p16 − OPSCC [8, 11, 12]. Even in cases with R1 status, p16 + OPSCC has better overall survival than R1/p16 − OPSCC. The present data confirm that p16 status is the decisive factor for the prognosis of a tumor disease involving OPSCC. In p16 + OPSCC, the difference in survival between patients with an R0 resection and those with an R1 resection of the tumor was significant in the univariate model but not after multivariate adjustment indicating that the observed poorer survival rates can be attributed to the fact that patients who underwent R1 resection had more advanced T stages.

Given the improved treatment response in p16 + OPSCC, the question arises as to whether treatment de-escalation might also be justified. Numerous studies are currently underway that address treatment de-escalation in p16 + OPSCC [19]. De-escalation is primarily achieved in non-surgical treatment approaches through a reduction in radiation dose or adapted delivery regimens, dose reductions in chemotherapy.

Several recent studies have concluded that reducing the resection margins in HPV-associated OPSCC to just a few millimeters while maintaining R0 resection is acceptable without compromising treatment success [20–24]. Many studies distinguish between an R1 resection and a close margin, noting that reducing the resection margin to up to 1 mm has no impact on overall survival, disease-free survival, or locoregional control, whereas an R1 status does [25–28].

To date, the standard for surgical treatment of OPSCC has been resection within the "old margins," even if macroscopic tumor reduction has been achieved through induction therapy. Resection within the "new margins" would carry the risk of leaving microscopic tumor remnants in the former tumor area that persist after induction. This would create a potential R1 situation, which, according to current knowledge, is considered a strong negative predictor of the success of surgical tumor therapy [25–29].

In the context of a potential R1 resection as part of surgical de-escalation, local tumor control in p16 + OPSCC is becoming increasingly important. The data from this analysis show that R1 resection was associated with a significantly increased risk of recurrence or progression in the univariate model but not in the multivariate model. Future studies should examine the aspect of local or locoregional control in greater detail than a retrospective analysis of cancer registry data is capable of doing.

This aspect is also relevant from a radiation oncology perspective. The recommendation for postoperative chemoradiotherapy in R1-status patients is based on the RTOG 9501 [30] and EORTC 22,931 [31] studies, in which HPV-positive tumors were significantly underrepresented, accounting for an estimated proportion of only about 17% [32] — a prospective validation of this recommendation for the p16 + cohort is thus still lacking to date. Our data show no significant difference in survival between R0 and R1 status in both, p16- and

p16 + OPSCC patients receiving postoperative radiation therapy. However, it should be noted that the vast majority of R1 patients in the cohort not only received chemoradiotherapy, but more intensive adjuvant therapy than R0 patients (p16+: systemic therapy 77.8% vs. 54.5%, mean dose 64.0 vs. 61.3 Gy; P16-: systemic therapy 78.9% vs. 51.4%, mean dose 65.2 Gy vs. 60.1 Gy). A compensatory effect of the more intensive postoperative therapy cannot be ruled out as there is a strong recommendation for chemotherapy in addition to radiotherapy for R1-patients in the German guidelines. Since R1 status was tested as a hard criterion for the indication of postoperative chemotherapy in large indication studies, particularly for p16 − tumors, there is an evidence gap regarding the relevance of chemotherapy in p16 + OPSCC, more so regarding the indication of intensification of radiation dose for R1-situations, which differs between institutions. Both aspects should be investigated prospectively.

There is also a current trend toward dose de-escalation in postoperative radiotherapy: The randomized Phase II study ECOG-ACRIN E3311 [33] showed in its long-term results that reducing postoperative radiation therapy from 60 to 50 Gy in intermediate-risk patients does not result in an increased late recurrence rate. Preliminary results show a 54-month progression-free survival rate of 90% [34].

The non-randomized Phase II MINT study [35] demonstrated that de-escalation to 42 Gy was compatible with a 4-year progression-free survival of 90% and significantly reduced toxicity, even in high-risk patients with positive resection margins.

The current ASTRO Clinical Practice Guideline 2024 [36] addresses p16 + OPSCC as a distinct entity for the first time; it continues to recommend chemoradiotherapy with cisplatin for R1, but this recommendation is also based on evidence that was not primarily generated for the HPV-associated cohort.

Based on a larger cohort, the present data provide further strong evidence that p16 status—and not just the resection margin—is the decisive prognostic factor in OPSCC, and underscore the need for prospective studies that specifically address the significance of R status in HPV-associated cohorts.

Data on overall survival in OPSCC and R1 status are now available from this study and differ from those in the cited studies. P16+OPSCC does not differ in overall survival with respect to R0 or R1 status when postoperative radiotherapy was administered. Overall survival is influenced more by p16 status as the decisive factor.

Reflections on surgical de-escalation

A true de-escalation of the surgical approach could, for example, involve resecting the primary tumor within its new boundaries following tumor reduction after induction therapy. Particularly in cases of tonsillar carcinoma extending to the soft palate, resection of the soft palate might be avoided under certain circumstances if, following induction therapy, the tumors were macroscopically confined solely to the tonsil. A plastic reconstruction of the soft palate might not be necessary, and functionality regarding voice quality, swallowing, and velopharyngeal closure could potentially be preserved. Against this backdrop, surgical de-escalation appears worth considering, even if it contradicts the previous standard of resection within the old margins. In an adapted study design, resection could be performed within the "new margins" following induction therapy, and a potential R1 situation could be deliberately accepted. This approach has not yet been pursued in surgical de-escalation studies, as initiating such surgical studies would pose ethical challenges. In principle, however, the study approach would correspond to the analyzed dataset of the present survey.

In light of the KEYNOTE 689 study [37], in which pembrolizumab is administered as perioperative induction therapy in two doses, the concept of surgical de-escalation should be further developed. The authors do not provide detailed information on the resection margins adhered to in the publication, but it is postulated that resection was performed within the original margins. Thus, this study also follows the approach of resection within the original margins. It is possible that in p16 + OPSCC, with induction therapy followed by resection within the "new margins" while accepting an R1 situation and subsequent radio(system)therapy, the negative predictive value of the resection status could lose its significance. The planned systemic radiotherapy would then be administered following a high-risk classification [32, 38], in which patients with an R1 resection would receive a higher radiation dose and more frequently undergo systemic therapy.

The data evaluated in this study suggest that patients with R1 status received, on average, a higher total radiation dose and were more likely to receive systemic therapy, although the specific treatment regimens could not be described in detail. However, it can be assumed that these patients received postoperative therapy according to a high-risk regimen. These considerations reframe rather than confirm a de-escalation concept. Resection within new margins, accepting higher rates of R1 situation, followed by a high-risk adjuvant regimen does not reduce overall treatment intensity; it shifts intensity from the surgical to the radiotherapeutic and systemic domain. The rationale for such an approach is therefore not a reduction of total treatment burden but the preservation of organ function at the primary site - potentially avoiding extended resection and reconstruction and their functional long-term effects. Whether this modality shift results in lower net toxicity or a benefit of quality-of-life cannot be inferred from overall-survival data and remains an open question for prospective evaluation.

Limitations of the study

When interpreting the study results, it should be critically noted that, in the population of 3,412 OPSCC cases, p16 status was not available for 971 cases (28.5%), even though, according to TNM 8, reporting of p16 status is or was mandatory for OPSCC cases with the corresponding ICD-10 code. It remains unclear to what extent these excluded patients would have influenced the survival curves. However, a potential bias due to the missing data cannot be ruled out.

In accordance with the research hypothesis and the resulting analysis design, it was only possible to include cohorts that underwent surgery followed by radiation therapy. It needs to be kept in mind that the exclusion of R0 patients who did not receive postoperative radiotherapy yielded a selected, higher-risk R0 group that might not be representative of typical R0 cases. Consequently, the comparison between the R0 and R1 groups may be biased and should be interpreted with caution.

Furthermore, the statistical power for certain comparisons (R1 vs. R0 status in p16- OPSCC) can be discussed as being too low to reveal true statistically significant differences. Thus, future analyses comprising a larger sample size would be desirable for this specific comparison. However, the statistical power is adequate to reveal significant differences in survival at least on the univariate level for the other three group comparisons.

The authors are aware of the acknowledged p16-HPV discordance. More confirmatory HPV-specific testing (PCR, DNA-ISH, RNA-ISH) or other parameters would have been desirable. Unfortunately, no additional HPV-specific or prognostic data could be collected beyond the p16 status. In Germany, there is a legal requirement to report cancer cases, and the analyzed data are based on this reporting system. For oropharyngeal carcinomas, the p16 status is a mandatory reporting item. Other HPV-specific testing methods are not subject to mandatory reporting and are therefore not available through the cancer registry. The same applies to other parameters such as smoking status, C-reactive protein, plasma albumin, quality of life or margin-distance data. Further prospective studies that collect this data should be conducted to test the hypotheses of the present analysis.

Dose of radiation and systemic therapy were included as covariates in the Cox models, so the adjusted result is not driven by confounding alone. That adjustment, however, is incomplete as the registry only records total radiation dose and whether systemic therapy was given or not. There are no regimen details available so the extent of treatment intensity is not fully captured. More importantly, R1 status and treatment intensification almost always occurred together, so the model cannot cleanly separate the two and more so given the small R1 groups (p16+n=54; p16−n=19). Chemotherapy in the R1 setting is, however, itself a guideline recommendation. We therefore cannot demonstrate an independent effect of margin status at equal treatment intensity which needs to be stated. Whether R0 and R1 in fact yield equivalent outcomes under comparable adjuvant therapy - and thus whether the overall treatment concept can genuinely be de-escalated - likewise requires prospective evaluation.

The patients included in the study all reside in the Berlin-Brandenburg region of Germany. Due to existing differences in the epidemiology and treatment of p16+OPSCC across different countries, the present data should not be extrapolated to other regions of the world without critical review.

Conclusion

Patients with p16+oropharyngeal squamous cell carcinoma (OPSCC) demonstrate improved overall survival compared to those with p16−OPSCC. The p16 status seems to be a stronger prognostic marker than the resection status following tumor resection. The observed poorer survival rates after R1 compared to R0 resection in p16+OPSCC in the univariate model can be attributed to the fact that patients who underwent R1 resection had more advanced T stages. In p16+OPSCC, there is no difference after multivariate adjustment between patients with an R0 resection and those with an R1 resection of the tumor with respect to the overall survival.

Based on the presented data, any de-intensification of surgery would, however, be coupled to an intensified adjuvant regimen and thus represents a redistribution rather than a reduction of treatment burden; its functional benefit requires prospective validation.

Therefore, the data presented should not be considered as a recommendation for surgical de-escalation, but rather as an incentive to initiate further prospective studies that address especially local and locoregional control, resection margins, specific HPV-testing, applied radiosystemic regimens and patients' quality of life.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00405-026-10539-8.

Acknowledgements This was supported by the State Working Group for Oncological Care Brandenburg (Landesarbeitsgemeinschaft Onkologische Versorgung Brandenburg e. V., No. 3.2.3; 12 Nov 2025).

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Compliance with ethical guidelines The study received approval from the Brandenburg State Medical Association on April 13, 2026.

References

1. Wilson DD, Crandley EF, Sim A et al (2014) Prognostic significance of p16 and its relationship with human papillomavirus in pharyngeal squamous cell carcinomas. JAMA Otolaryngol Head Neck Surg 140:647–653. https://doi.org/10.1001/jamaoto.2014.821
2. Wittekindt C, Wagner S, Bushnak A et al (2019) Increasing Incidence rates of Oropharyngeal Squamous Cell Carcinoma in Germany and Significance of Disease Burden Attributed to Human Papillomavirus. Cancer Prev Res (Phila) 12:375–382. https://doi.org/10.1158/1940-6207.CAPR-19-0098
3. Suchan M, Wuerdemann N, Sharma SJ et al (2021) Das HPV-positive Oropharynxkarzinom – eine Entität mit steigender Inzidenz (HPV-related oropharyngeal squamous cell carcinoma-Incidence steadily rising). HNO 69:599–608. https://doi.org/10.1007/s00106-021-01087-0
4. Tinhofer I, Jöhrens K, Keilholz U et al (2015) Contribution of human papilloma virus to the incidence of squamous cell carcinoma of the head and neck in a European population with high smoking prevalence. Eur J Cancer 51:514–521. https://doi.org/10.1016/j.ejca.2014.12.018
5. Liao C-I, Francoeur AA, Kapp DS et al (2022) Trends in Human Papillomavirus-Associated Cancers, Demographic Characteristics, and Vaccinations in the US, 2001–2017. JAMA Netw Open 5:e222530. https://doi.org/10.1001/jamanetworkopen.2022.2530
6. Ang KK, Harris J, Wheeler R et al (2010) Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 363:24–35. https://doi.org/10.1056/NEJMoa0912217
7. Budach V, Tinhofer I (2019) Novel prognostic clinical factors and biomarkers for outcome prediction in head and neck cancer: a systematic review. Lancet Oncol 20:e313–e326. https://doi.org/10.1016/S1470-2045(19)30177-9
8. Rahimi S (2020) HPV-related squamous cell carcinoma of oropharynx: a review. J Clin Pathol 73:624–629. https://doi.org/10.1136/jclinpath-2020-206686
9. Kass JI, Giraldez L, Gooding W et al (2016) Oncologic outcomes of surgically treated early-stage oropharyngeal squamous cell carcinoma. Head Neck 38:1467–1471. https://doi.org/10.1002/hed.24456
10. Mehanna H, Taberna M, von Buchwald C et al (2023) Prognostic implications of p16 and HPV discordance in oropharyngeal cancer (HNCIG-EPIC-OPC): a multicentre, multinational, individual patient data analysis. Lancet Oncol 24:239–251. https://doi.org/10.1016/S1470-2045(23)00013-X
11. Wang MB, Liu IY, Gornbein JA et al (2015) HPV-Positive Oropharyngeal Carcinoma: A Systematic Review of Treatment and Prognosis. Otolaryngol Head Neck Surg 153:758–769. https://doi.org/10.1177/0194599815592157
12. Sinha P, Karadaghy OA, Doering MM et al (2018) Survival for HPV-positive oropharyngeal squamous cell carcinoma with surgical versus non-surgical treatment approach: A systematic review and meta-analysis. Oral Oncol 86:121–131. https://doi.org/10.1016/j.oraloncology.2018.09.018
13. Mansour N, Backes C, Becker C et al (2021) Sichere R0-Resektion zur Vermeidung der adjuvanten Therapieeskalation beim Oropharynxkarzinom (Clear resection margins to avoid escalation of adjuvant therapy in oropharyngeal squamous cell carcinoma). HNO 69:256–262. https://doi.org/10.1007/s00106-020-00932-y
14. Eldeeb H, Macmillan C, Elwell C et al (2012) The effect of the surgical margins on the outcome of patients with head and neck squamous cell carcinoma: single institution experience. Cancer Biol Med 9:29–33. https://doi.org/10.3969/j.issn.2095-3941.2012.01.005
15. Kumar B, Cipolla MJ, Old MO et al (2016) Surgical management of oropharyngeal squamous cell carcinoma: Survival and functional outcomes. Head Neck 38 Suppl 1E1794–E1802. https://doi.org/10.1002/hed.24319
16. Kurita H, Nakanishi Y, Nishizawa R et al (2010) Impact of different surgical margin conditions on local recurrence of oral squamous cell carcinoma. Oral Oncol 46:814–817. https://doi.org/10.1016/j.oraloncology.2010.08.014
17. Woolgar JA, Scott J, Vaughan ED et al (1995) Survival, metastasis and recurrence of oral cancer in relation to pathological features. Ann R Coll Surg Engl 77:325–331
18. Amin MB, Greene FL, Edge SB et al (2017) The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more personalized approach to cancer staging. CA Cancer J Clin 67:93–99. https://doi.org/10.3322/caac.21388
19. Chen AM (2025) De-escalation for Human Papillomavirus-Positive Oropharyngeal Cancer: A Look at the Prospective Evidence. Curr Oncol Rep 27:355–361. https://doi.org/10.1007/s11912-025-01652-8
20. Ausburn M, Pyne JM, Day AT et al (2025) Margin Status and Recurrence in Surgically Treated Patients With HPV+ Oropharyngeal Cancer. Laryngoscope 135:2777–2782. https://doi.org/10.1002/lary.32091
21. Karadaghy OA, Wu MP, Farrokhian N et al (2025) Impact of Margins on Outcomes in HPV-Related Oropharyngeal Squamous Cell Carcinoma Treated With Surgery Only. Otolaryngol Head Neck Surg 173:106–114. https://doi.org/10.1002/ohn.1213
22. den Besten C, Hathi K, MacKay C et al (2025) Close then clear" margins in transoral resection of p16+oropharyngeal squamous cell carcinoma. Otolaryngol Head Neck Surg 173:1432–1439. https://doi.org/10.1002/ohn.70032
23. Holsinger FC, Ismaila N, Adkins DR et al (2025) Transoral Robotic Surgery in the Multidisciplinary Care of Patients With Oropharyngeal Squamous Cell Carcinoma: ASCO Guideline. J Clin Oncol 43:1369–1392. https://doi.org/10.1200/JCO-24-02755
24. Park YM, Lim J-Y, Koh YW et al (2023) Surgical margin status and role of adjuvant therapy in human papillomavirus-positive oropharyngeal cancer. Head Neck 45:2369–2376. https://doi.org/10.1002/hed.27473
25. Chua BQY, Chong VWS, Kadir HBA et al (2025) Histopathological Prognostic Factors of Surgically Treated HPV-Associated Oropharyngeal Squamous Cell Carcinoma: A Systematic Review and Meta-analysis. Ann Surg Oncol 32:1280–1300. https://doi.org/10.1245/s10434-024-16362-x
26. O'Hara J, Warner L, Fox H et al (2021) Primary transoral robotic surgery +/- adjuvant therapy for oropharyngeal squamous cell carcinoma-A large observational single-centre series from the United Kingdom. Clin Otolaryngol 46:1005–1012. https://doi.org/10.1111/coa.13769
27. Kornfeld B, Taha A, Kyang L et al (2024) Oncological outcomes post transoral robotic surgery (TORS) for HPV-associated oropharyngeal squamous cell carcinoma, a single-centre retrospective Australian study. J Robot Surg 18:226. https://doi.org/10.1007/s11701-024-01910-0
28. Calcano GA, Rourk KS, Routman DM et al (2025) The Impact of Close Margins in HPV-Associated Oropharyngeal Squamous Cell Carcinoma Treated With TORS. Otolaryngol Head Neck Surg 172:1291–1299. https://doi.org/10.1002/ohn.1127
29. Williamson A, Moen CM, Slim MAM et al (2023) Transoral robotic surgery without adjuvant therapy: A systematic review and meta-analysis of the association between surgical margins and local recurrence. Oral Oncol 147:106610. https://doi.org/10.1016/j.oraloncology.2023.106610
30. Cooper JS, Pajak TF, Forastiere AA et al (2004) Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 350:1937–1944. https://doi.org/10.1056/NEJMoa032646

31. Bernier J, Domenge C, Ozsahin M et al (2004) Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med 350:1945–1952. https://doi.org/10.1056/NEJMoa032641
32. Cooper JS, Fortpied C, Gregoire V et al (2017) The role of postoperative chemoradiation for oropharynx carcinoma: A critical appraisal revisited. Cancer 123:12–16. https://doi.org/10.1002/cncr.30266
33. Ferris RL, Flamand Y, Weinstein GS et al (2022) Phase II Randomized Trial of Transoral Surgery and Low-Dose Intensity Modulated Radiation Therapy in Resectable p16+Locally Advanced Oropharynx Cancer: An ECOG-ACRIN Cancer Research Group Trial (E3311). J Clin Oncol 40:138–149. https://doi.org/10.1200/JCO.21.01752
34. Burtness B, Flamand Y, Quon H et al (2025) Long-Term Follow-Up of E3311, an ECOG-ACRIN Cancer Research Group Phase II Trial of Transoral Surgery and Risk-Based Adjuvant Treatment in Human Papillomavirus-Initiated Oropharynx Cancer. J Clin Oncol 43:2559–2565. https://doi.org/10.1200/JCO-24-02550
35. Thorstad WL, Jackson RS, Oppelt P et al (2024) Long-Term Efficacy of Risk-Directed, De-Escalated Post-Operative Adjuvant Therapy for Surgically Resected Locally Advanced, Human Papillomavirus-Positive Oropharynx Squamous-Cell Carcinoma (HPV+ OPSCC): A Non-Randomized, Multi-Arm Phase 2 Trial. Int J Radiation Oncology*Biology*Physics 118:e10. https://doi.org/10.1016/j.ijrobp.2024.01.029
36. Margalit DN, Anker CJ, Aristophanous M et al (2024) Radiation Therapy for HPV-Positive Oropharyngeal Squamous Cell Carcinoma: An ASTRO Clinical Practice Guideline. Pract Radiat Oncol 14:398–425. https://doi.org/10.1016/j.prro.2024.05.007
37. Uppaluri R, Haddad RI, Adkins D (2025) Perioperative Pembrolizumab in Head and Neck Cancer. Reply. N Engl J Med 393:1138–1139. https://doi.org/10.1056/NEJMc2510882
38. Bernier J, Cooper JS, Pajak TF et al (2005) Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck 27:843–850. https://doi.org/10.1002/hed.20279