

Human Papillomavirus and Overall Survival After Progression of Oropharyngeal Squamous Cell Carcinoma

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See accompanying editorial on page 3349; listen to the podcast by Dr Wirth at www.jco.org/podcasts

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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ABSTRACT

Purpose

Risk of cancer progression is reduced for patients with human papillomavirus (HPV) –positive oropharynx cancer (OPC) relative to HPV-negative OPC, but it is unknown whether risk of death after progression is similarly reduced.

Patients and Methods

Patients with stage III-IV OPC enrolled onto Radiation Therapy Oncology Group trials 0129 or RTOG 0522 who had known tumor p16 status plus local, regional, and/or distant progression after receiving platinum-based chemoradiotherapy were eligible for a retrospective analysis of the association between tumor p16 status and overall survival (OS) after disease progression. Rates were estimated by Kaplan-Meier method and compared by log-rank; hazard ratios (HRs) were estimated by Cox models. Tests and models were stratified by treatment protocol.

Results

A total of 181 patients with p16-positive ($n = 105$) or p16-negative ($n = 76$) OPC were included in the analysis. Patterns of failure and median time to progression (8.2 v 7.3 months; $P = .67$) were similar for patients with p16-positive and p16-negative tumors. After a median follow-up period of 4.0 years after disease progression, patients with p16-positive OPC had significantly improved survival rates compared with p16-negative patients (2-year OS, 54.6% v 27.6%; median, 2.6 v 0.8 years; $P < .001$). p16-positive tumor status (HR, 0.48; 95% CI, 0.31 to 0.74) and receipt of salvage surgery (HR, 0.48; 95% CI, 0.27 to 0.84) reduced risk of death after disease progression whereas distant versus locoregional progression (HR, 1.99; 95% CI, 1.28 to 3.09) increased risk, after adjustment for tumor stage and cigarette pack-years at enrollment.

Conclusion

Tumor HPV status is a strong and independent predictor of OS after disease progression and should be a stratification factor for clinical trials for patients with recurrent or metastatic OPC.

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INTRODUCTION

Human papillomavirus (HPV) is the cause of a subset of oropharyngeal squamous cell carcinomas (OPCs), and tumor HPV status is a strong and independent biomarker for prognosis. The risk of cancer progression for patients with HPV-positive OPC is significantly reduced compared with patients with HPV-negative OPC.¹⁻² Nevertheless, 10% to 25% of patients with HPV-positive OPC experience disease progression within 3 years of completing primary therapy.^{1,3-7} Whether the survival benefit experienced by patients with HPV-positive versus HPV-negative

OPC continues after disease progression is currently unknown.

Data from prospective clinical trials indicate that patients with HPV-positive OPC have reduced rates of locoregional failure, but not distant metastases, relative to patients with HPV-negative OPC.^{1,4} Retrospective analyses and case reports have reported unusual patterns of disease progression for HPV-positive OPC, including late failures, unusual anatomic site distributions or a “disseminated” pattern of distant metastases.⁸⁻¹¹ Because of the potential for ascertainment or reporting bias, these findings should be confirmed in a prospective clinical trial.

HPV-positive OPC is a newly identified and unique clinical entity with increasing incidence in the United States.¹² Because of the strong prognostic advantage associated with HPV-positive OPC, disease progression may be unexpected. Currently, few data are available to counsel patients regarding expectations for survival after disease progression. Such data will also have important implications for clinical trial design in this patient population. Here, we examine the influence of tumor HPV status on patterns of failure and survival after disease progression within prospective clinical trials conducted by the Radiation Therapy Oncology Group (RTOG).

PATIENTS AND METHODS

Protocol and Treatment

RTOG trials 0129 and RTOG 0522 were phase III clinical trials designed to evaluate whether accelerated fractionation by concomitant boost (AFX-C) in comparison to standard fractionation (SFX) radiotherapy improves overall survival (OS) rates of head and neck cancer patients treated with concurrent high-dose cisplatin, and whether adding cetuximab to cisplatin with AFX-C radiotherapy could improve progression-free survival, respectively. The primary results of both trials have been published.^{1,13-14}

Eligible patients for RTOG 0129 and RTOG 0522 had untreated, pathologically confirmed, stage III-IV¹⁵ squamous cell carcinoma of the oral cavity (RTOG 0129 only), oropharynx, hypopharynx, or larynx; Zubrod performance status 0 to 1; age \geq 18 years; and adequate bone marrow, hepatic, and renal function. Patients were stratified by tumor site (larynx ν other), nodal stage (N0 ν N1-N2b ν N2c-N3), and Zubrod performance status (0 ν 1). Patients in RTOG 0522 only were also stratified by use of intensity-modulated radiotherapy (IMRT; yes ν no) and receipt of pretreatment positron emission tomography/computed tomography scan (yes ν no).

Patients in RTOG 0129 were randomly assigned to receive cisplatin concurrent with either SFX (70 Gy in 35 fractions [fx], 2 Gy/fx, over 7 weeks) or AFX-C (72 Gy delivered in 42 fx over 6 weeks, inclusive of twice-per-day irradiation for 12 treatment days). Patients in RTOG 0522 were randomly assigned to receive cisplatin concurrent with or without cetuximab with AFX-C (as in the case of patients in RTOG 0129, except with IMRT 70 Gy in 35 fx, 2 Gy/fx, over 6 weeks, 6 fx/week). Chemotherapy consisted of intravenous cisplatin 100 mg/m² of body-surface area for SFX (days 1, 22, and 43) and AFX-C (days 1 and 22). Cetuximab dose was intravenous 400 mg/m² the week before radiotherapy, then 250 mg/m² weekly during radiotherapy.¹⁶

History of cigarette smoking in pack-years was obtained at enrollment via interviewer-administered questionnaire. To assess disease status, follow-up examinations and imaging studies were performed four times per year for 2 years, twice per year through year 5, and once per year thereafter.

Patients eligible for this analysis included patients with OPC who were enrolled onto RTOG trials 0129 or RTOG 0522 with evaluable p16 expression status (a surrogate of HPV tumor status) and disease progression (local, regional, or distant) during the follow-up period.

Laboratory Analysis

Tumor p16 expression was evaluated by immunohistochemistry using a mouse monoclonal antibody (MTM Laboratories, Heidelberg, Germany) and was visualized with the Ventana XT autostainer using the I-view secondary detection kit (Ventana, Tuscon, AZ).¹⁷ p16 expression was scored as positive if strong and diffuse nuclear and cytoplasmic staining was present in at least 70% of the tumor cells.¹⁸⁻¹⁹ Testing and interpretation were centralized.

Statistical Analysis

Disease progression was defined as evidence of local, regional, or distant disease related to OPC. Salvage surgery was defined as resection of local, regional, or distant disease within 6 weeks of documented progression (independent of radiotherapy completion date). To evaluate potential biases introduced by missing data, we compared patient and tumor characteristics plus survival rates after progression for OPC patients with known and unknown

p16 expression status. We also compared categorical variables using Fisher's exact test and ordinal or continuous variables using the Wilcoxon rank-sum test. We compared time from randomization to progression between the p16-positive and p16-negative groups using the Wilcoxon rank-sum test.

The principal outcome of interest was OS after disease progression, calculated as time from first disease progression event to death or last follow-up. Survival rates were estimated using the Kaplan-Meier method²⁰ and were compared using a two-sided stratified (by trial) log-rank test.²¹ Hazard ratios were estimated by Cox proportional hazards model stratified²² by trial. Multivariable models were compared using Akaike information criterion (AIC). Models with AIC within two of the minimum AIC were considered sufficiently similar to warrant consideration as the final model. p16 status, age, sex, race, Zubrod performance status, anemia, pack-years, T stage, N stage, protocol therapy, salvage surgery, and site of progression were considered for inclusion in the multivariable model. A sensitivity analysis evaluated salvage surgery at any time after progression as a time-dependent covariate. Potential interactions between p16 tumor status and both progression type and surgical salvage were explored with multivariable modeling. To investigate potential bias in estimates owing to missing pack-years, we repeated analysis of the final model using values imputed with the Markov chain Monte Carlo algorithm with a noninformative prior distribution. Twenty data sets were created, and the resulting analyses were combined per Rubin's formula.²³

RESULTS

Characteristics of the Study Population

A total of 1,058 eligible patients with OPC were randomly assigned to receive protocol therapy in RTOG 0129 (n = 433) from July 2002 to June 2005 and RTOG 0522 (n = 625) from November 2005 to March 2009. Of these, 637 patients had evaluable p16 tumor status. Disease progression occurred among 105 (23.3%) of 450 p16-positive patients versus 76 (40.6%) of 187 p16-negative patients ($P < .001$; Fig 1). These 181 patients with disease progression and available tumor p16 status comprised the study population. The characteristics and treatment outcomes for patients with OPC (n = 309) who experienced disease progression with evaluable p16 tumor status (n = 181) and without (n = 128) were similar (Appendix Table A1; Appendix Fig A1 [online-only]).

The study population included 95 patients from RTOG 0129 and 86 patients from RTOG 0522. At enrollment in the original protocols, patients' median age was 56 years (interquartile range, 51 to 62). The majority of the patients were men (87.8%) and had American Joint Committee on Cancer stage IV disease (93.4%; T4, 35.4%; N2b-N3, 77.3%). Median pack-years of cigarette smoking at enrollment was 23.8 pack-years (IQR, 4.5 to 45 pack-years).

Of the 181 patients, 105 (58%) patients had p16-positive tumors and 76 (42%) had p16-negative tumors. Despite disease progression, patients with p16-positive tumors were significantly more likely than patients with p16-negative tumors to be younger, of white race, report less cumulative cigarette exposure, and present with a smaller (ie, earlier tumor stage) tumor of the tonsil or base of tongue at enrollment (Table 1). p16-positive patients received a greater number of cycles of cisplatin during primary therapy, although this was not statistically significant.

Patterns of Disease Progression

The median time to disease progression was similar for p16-positive and p16-negative patients (8.2 ν 7.3 months; $P = .67$). The majority of p16-positive and p16-negative patients had disease progression within the first year after protocol therapy (65% ν 63%) and

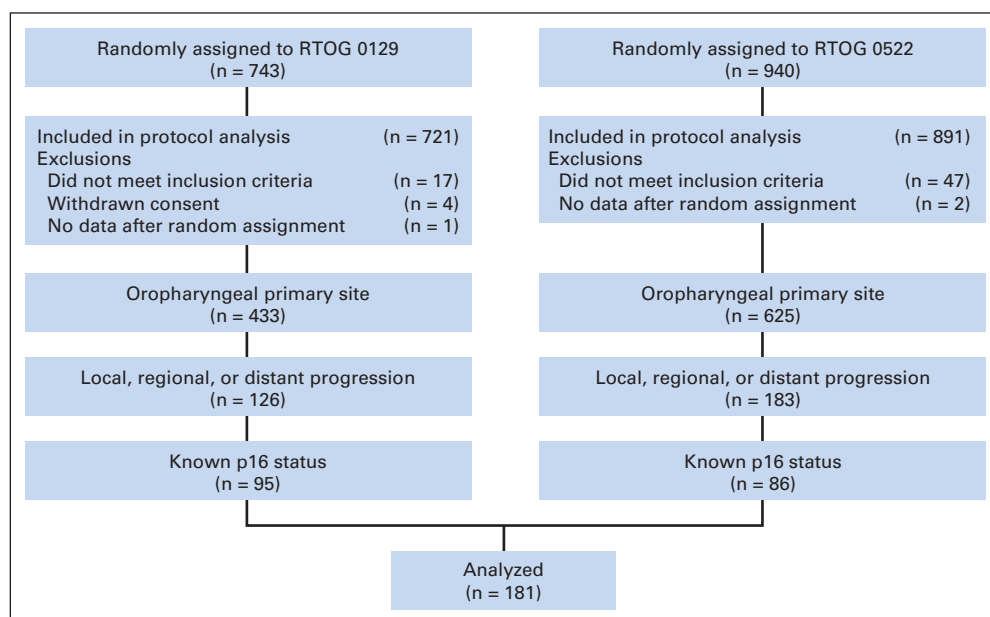


Fig 1. CONSORT diagram. RTOG, Radiation Therapy Oncology Group.

in similar proportions each year thereafter (within the first 2 years, 82% v 86%; within the first 3 years, 86% v 93%).

The first sites of disease progression for the 181 patients were locoregional only ($n = 100$; 55.2%), distant metastases only ($n = 72$; 39.8%), or both ($n = 9$; 5.0%). The patterns of disease progression for p16-positive and p16-negative patients are compared in Table 1. Similar percentages of patients had distant metastases (with or without locoregional progression): 48 (45.7%) of 105 patients whose disease was p16 positive and 33 (43.4%) of 76 patients whose disease was p16 negative ($P = .76$; Table 1). The anatomic site distribution of distant metastases was also similar in the two groups. Of the 81 patients with distant metastases, the percentage of p16-positive and p16-negative patients who had lung (72.9% v 69.7%; $P = .75$), bone (14.6% v 15.2%), liver (8.3% v 15.2%), or other (16.7% v 12.1%) metastases was similar.

We also compared patterns of disease progression among patients with OPC categorized as having low, intermediate, or high risk of death based on their tumor p16 status, number of pack-years, and T and N stage, as defined in RTOG 0129.¹ Of the OPC patients enrolled onto RTOG 0129 and RTOG 0522, 547 of 1,058 patients had available p16 tumor status and cigarette pack-years and were classified as having low ($n = 263$), intermediate ($n = 166$), or high risk ($n = 118$) of death. Disease progression was observed among 49 (18.6%) of 263 patients in the low-risk group, 54 (32.5%) of 166 patients in the intermediate-risk group, and 51 (43.2%) of 118 patients in the high-risk group. Patterns of disease progression are listed in Table 2. Among the patients with disease progression, the proportion of patients in the intermediate-risk group who had distant metastases (30 [55.6%] of 54 patients) was higher than in the low-risk group (38.8%) and high-risk (41.2%) group; however, this was not statistically significant ($P = .18$).

Survival Analysis

The median follow-up time after first event of disease progression among surviving patients ($n = 58$) was 4.0 years (range, 0.04 to 8.97). At the time of analysis, 123 (68.0%) of 181 patients had died,

including 61 (58.1%) of 105 p16-positive patients and 62 (81.6%) of 76 p16-negative patients. The cause of death was index cancer for 81 (65.9%) of 123 patients, second primary for 14 (11.4%) of 123 patients, or other/unknown cause for 28 (22.8%) of 123 patients, and these did not differ by p16 tumor status ($P = .34$).

In Kaplan-Meier analysis, p16-positive patients had significantly improved OS after disease progression when compared with p16-negative patients (hazard ratio [HR], 0.49; 95% CI, 0.34 to 0.70; $P < .001$; Fig 2). Estimated median OS after progression was 2.6 years (95% CI, 1.5 to 5.1) versus 0.8 years (95% CI, 0.6 to 0.9) for p16-positive versus p16-negative patients, respectively. Estimated 2-year OS after progression was 54.6% for patients with p16-positive tumors (95% CI, 44.9% to 64.4%) and 27.6% for patients with p16-negative tumors (95% CI, 17.3% to 37.9%).

Additional factors associated with OS after disease progression in univariable analysis are listed in Table 3. Patient characteristics at protocol enrollment associated with OS after progression included age, performance status, anemia, and advanced tumor stage. Cumulative measures of cigarette smoking at enrollment were available for 154 (85.1%) of 181 patients. Among these patients, individuals with more than 20 pack-years of cigarette use had a significantly increased risk of death after disease progression, and the risk of death increased by 1% per pack-year (HR, 1.01; 95% CI, 1.0 to 1.02; $P = .002$).

After protocol enrollment, fewer on-protocol cisplatin cycles significantly increased the risk of death after progression. At the time of disease progression, distant metastases compared with locoregional disease progression also significantly increased the risk of death (distant v locoregional: HR, 2.03; 95% CI, 1.41 to 2.90; $P < .001$).

After disease progression, 49 of 181 patients overall, and a similar proportion of p16-positive or p16-negative patients (27.6 v 26.3%; $P = .85$), underwent salvage surgery. The characteristics of patients who did and did not undergo salvage surgery were similar (Appendix Table A2), except for their mean age (56.8 v 54.2 years; $P = .05$). The majority (28 of 49 patients) underwent surgery more than 4 months

Table 1. Patient and Tumor Characteristics by p16 Tumor Status

Characteristic	p16 Negative (n = 76)		p16 Positive (n = 105)		P
	No. of Patients	%	No. of Patients	%	
Protocol					.07*
RTOG 0129	46	60.5	49	46.7	
RTOG 0522	30	39.5	56	53.3	
Age at enrollment, years					.01†
Median	58.5		53		
Range	37-79		36-75		
Sex					.11*
Male	63	82.9	96	91.4	
Female	13	17.1	9	8.6	
Race					.002*
Asian	2	2.6	0	0.0	
Black or African American	15	19.7	6	5.7	
White	59	77.6	98	93.3	
Unknown	0	0.0	1	1.0	
Zubrod PS at enrollment					.76*
0	43	56.6	62	59.0	
1	33	43.4	43	41.0	
Anemic at enrollment‡					.08*
No	45	59.2	76	72.4	
Yes	31	40.8	29	27.6	
Smoking history, pack-years§	58		96		< .001†
Median, range	38.5		16.5		
Range	0-104		0-81		
Primary site at enrollment					.02*
Oropharynx NOS	9	11.8	14	13.3	
Faucial arch	1	1.3	0	0.0	
Tonsillar fossa or tonsil	19	25.0	39	37.1	
Base of tongue	36	47.4	52	49.5	
Pharyngeal oropharynx	8	10.5	0	0.0	
Soft palate	3	3.9	0	0.0	
T stage at enrollment					.02†
T2	19	25.0	43	41.0	
T3	24	31.6	31	29.5	
T4	33	43.4	31	29.5	
N stage at enrollment					.99†
N0	3	3.9	6	5.7	
N1	10	13.2	7	6.7	
N2a	8	10.5	7	6.7	
N2b	20	26.3	45	42.9	
N2c	26	34.2	26	24.8	
N3	9	11.8	14	13.3	
AJCC stage at enrollment					.56*
III	6	7.9	6	5.7	
IV	70	92.1	99	94.3	
On-protocol RT dose, Gy					.07†
Median	70		70		
Range	68-73.8		0-75.9		
On-protocol cisplatin cycles					.06†
0	2	2.6	1	1.0	
1	9	11.8	4	3.8	
2	55	72.4	81	77.1	
3	10	13.2	19	18.1	
First type of disease progression					.76*
Local	25	32.9	21	20.0	
Regional	14	18.4	32	30.5	
Local and regional	4	5.3	4	3.8	
Local and distant	3	3.9	3	2.9	
Regional and distant	1	1.3	2	1.9	
Distant	29	38.2	43	41.0	

(continued on following page)

HPV, Oropharyngeal Carcinoma Progression, and Overall Survival

Table 1. Patient and Tumor Characteristics by p16 Tumor Status (continued)

Characteristic	p16 Negative (n = 76)		p16 Positive (n = 105)		P
	No. of Patients	%	No. of Patients	%	
Salvage surgery within 6 weeks after progression					.87*
No	56	73.7	76	72.4	
Yes	20	26.3	29	27.6	
Cause of death	62		61		.34*
This disease (local, regional, or distant)	38	61.3	43	70.5	
Second primary or other malignancy	9	14.5	5	8.2	
Other cause	5	8.1	5	8.2	
Unknown	10	16.1	8	13.1	

Abbreviations: AJCC, American Joint Committee on Cancer, 5th edition (for RTOG 0129) or 6th Edition (for RTOG 0522); NOS, not otherwise specified; PS, performance status; RT, radiation therapy; RTOG, Radiation Therapy Oncology Group.

*Fisher's exact test. All non-white races were combined. Primary site was tested as tonsil or base of tongue versus others. Progression type was tested as distant (± locoregional) versus locoregional only. Cause of death was tested as a result of this disease versus other categories.

†Wilcoxon rank-sum test.

‡Anemia is defined as a hemoglobin level of 13.5 g per deciliter or less for men and 12.5 g per deciliter or less for women.

§A pack-year is defined as the equivalent of smoking one pack of cigarettes per day for 1 year.

after completing radiotherapy. The majority of the salvage surgeries performed was for local (19 [41.3%] of 46 surgeries) or regional (24 [52.2%] of 46 surgeries) disease progression, and these rates were not significantly different ($P = .40$). Median time to surgical salvage was similar for p16-positive patients (median, 136 days; range, 17 to 1,200 days) and p16-negative patients (median, 122.5 days; range, 58 to 349 days). Importantly, patients who underwent salvage surgery after disease progression had a significantly decreased risk of death after progression (HR, 0.44; 95% CI, 0.28 to 0.68; $P < .001$).

Factors independently associated with OS after disease progression in multivariable analyses included p16 tumor status, tumor stage, and cigarette pack-years at enrollment, as well as progression type (distant v locoregional) and salvage surgery (Table 4). When compared with patients with p16-negative tumors, patients with p16-positive tumors had an estimated 52% reduction in risk of death after adjustment for other factors (HR, 0.48; 95% CI, 0.31 to 0.74). When

compared with patients who did not undergo surgical salvage, patients who had surgical salvage had an estimated 52% reduction in the risk of death after disease progression (HR, 0.48; 95% CI, 0.27 to 0.84). Sensitivity analyses considering surgical salvage at any time as a time-dependent covariate yielded similar results (HR, 0.54; 95% CI, 0.31 to 0.93). In contrast, patients with distant metastases had a two-fold increase in risk of death (HR, 1.99; 95% CI, 1.28 to 3.09) compared with patients who had locoregional progression. Sensitivity analyses that included imputations for patients with missing smoking status revealed similar results. Estimates of risk of death remained robust when enrollment age, race, and nodal stage were included in the model (Appendix Table A3).

We evaluated potential interactions between p16 tumor status and both progression type and surgical salvage. Kaplan-Meier curves for OS stratified by progression type and surgical salvage are shown in Figure 3, stratified by p16 tumor status. The independent effect of p16

Table 2. Patterns of Disease Progression for Low-, Intermediate-, and High- Risk Groups (per RTOG 0129)

Pattern	Low Risk*		Intermediate Risk†		High Risk‡	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
All patients	263	48.1	166	30.3	118	21.6
Disease progression						
Yes	49	18.6	54	32.5	51	43.2
No	214	81.4	112	67.5	67	56.8
First type of disease progression	49		54		51	
Local	11	22.4	7	13.0	15	29.4
Regional	16	32.7	16	29.6	12	23.5
Local and regional	3	6.1	1	1.9	3	5.9
Local and distant	1	2.0	2	3.7	3	5.9
Regional and distant	1	2.0	0	0.0	1	2.0
Distant	17	34.7	28	51.9	17	33.3
Lung metastasis	19		30		21	
No	7	36.8	6	20.0	7	33.3
Yes	12	63.2	24	80.0	14	66.7

Abbreviation: RTOG, Radiation Therapy Oncology Group.

*Low risk: p16 positive and ≤ 10 pack-years, or p16 positive and > 10 pack-years and N0-N2a.

†Intermediate-risk: p16 positive, > 10 pack-years, and N2b-N3, or p16 negative, ≤ 10 pack-years, and T2-T3.

‡High-risk: p16 negative, ≤ 10 pack-years, and T4, or p16 negative and > 10 pack-years.

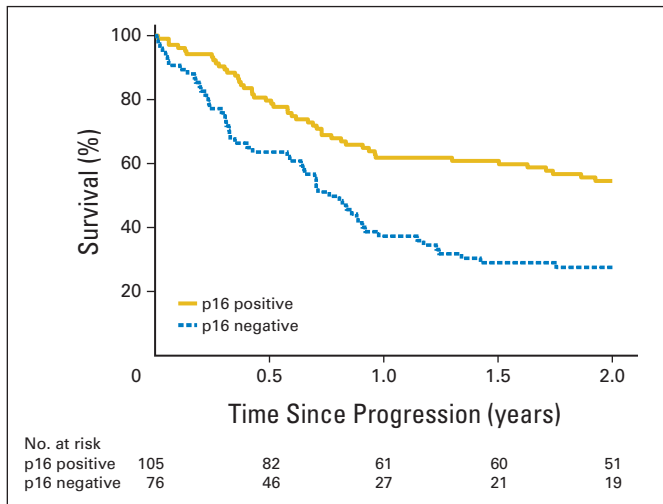


Fig 2. Kaplan-Meier estimates of overall survival after disease progression for patients with p16-positive and p16-negative oropharyngeal carcinoma (OPC). Patients with p16-positive OPC had significantly better overall survival after disease progression than patients with p16-negative OPC ($P < .001$). The 2-year rates of overall survival after disease progression were 54.6% for patients with p16-positive OPC (95% CI, 44.9 to 64.4) and 27.6% for patients with p16-negative OPC (95% CI, 17.3 to 37.9).

tumor status on survival appeared greater for patients with locoregional progression (HR, 0.34; 95% CI, 0.18 to 0.63) than for distant progression (HR, 0.66; 95% CI, 0.36 to 1.19), but this interaction did not reach statistical significance after adjustment for other factors ($P = .12$). The independent effect of p16 tumor status on survival also seemed greater for patients who underwent surgical salvage (HR, 0.26; 95% CI, 0.10 to 0.68) than for those who did not (HR, 0.55; 95% CI, 0.34 to 0.90), but this interaction did not reach statistical significance ($P = .16$).

Table 3. Univariable Analysis of Overall Survival in Oropharyngeal Cancer Patients With Disease Progression

Variable	HR	95% CI	<i>P</i>
All patients (n = 181; 123 events)			
p16 status (positive v negative)	0.49	0.34 to 0.70	< .001
Age at enrollment (> 55 v ≤ 55)	1.76	1.22 to 2.54	.002
Sex (male v female)	1.22	0.72 to 2.09	.46
Race (non-white v white)	1.22	0.75 to 2.00	.42
Zubrod PS at enrollment (1 v 0)	1.52	1.06 to 2.18	.02
Anemic at enrollment (yes v no)	1.47	1.02 to 2.13	.04
T stage at enrollment (T4 v T2-T3)	2.02	1.41 to 2.91	< .001
N stage at enrollment (N2b-N3 v N0-N2a)	1.27	0.82 to 1.98	.29
On protocol cisplatin cycles (0-1 v 2-3)	2.16	1.25 to 3.74	.006
Progression type (distant v locoregional)	2.03	1.41 to 2.90	< .001
Salvage surgery (yes v no)	0.44	0.28 to 0.68	< .001
Patients with known pack-years (n = 154; 100 events)			
Pack-years (continuous)	1.01	1.00 to 1.02	.002
Pack-years (> 10 v ≤ 10)	1.40	0.88 to 2.23	.15
Pack-years (> 20 v ≤ 20)	2.01	1.32 to 3.07	.001

Abbreviations: HR, hazard ratio from Cox proportional hazards model stratified by protocol; PS, performance status.

DISCUSSION

Patients with p16-positive OPC are significantly less likely to experience cancer progression after chemoradiotherapy than patients with p16-negative OPC. In this article, we demonstrate that tumor p16 status is also strongly associated with OS among OPC patients after disease progression. Median survival after disease progression was almost 2 years longer for patients with p16-positive versus p16-negative OPC (median, 2.6 v 0.8 years). Importantly, surgical salvage significantly improved OS for both patient groups. Our data have several important implications for clinical trial design, salvage therapy, diagnostic evaluation, and patient counseling.

Clinical trials for patients with recurrent or metastatic OPC currently do not consider the impact of tumor p16 status on study outcomes. The marked difference in survival rates between p16-positive and p16-negative OPC observed in our study indicates that tumor p16 status must be a stratification factor for clinical trials for recurrent and metastatic OPC. Retrospective analyses indicate response rates to palliative chemotherapy may be higher for patients with p16-positive than p16-negative OPC.²⁴ Indeed, the Eastern Cooperative Oncology Group observed higher response rates to platinum-based palliative chemotherapy and a trend toward improved survival for patients with p16-positive than p16-negative head and neck cancer.²⁵ Because of nonuniform treatment after disease progression and a lack of data collection regarding use and type of palliative chemotherapy in RTOG 0129 and RTOG 0522, we were unable to address the influence of chemotherapy on observed survival differences. We considered whether surrogates of improved performance status (age, anemia, and cisplatin cycles) may have accounted for improved OS; however, these factors did not influence point estimates in multivariable analysis (data not shown). HPV-positive tumors may inherently be biologically more responsive to therapy because of differences in p53,²⁶ p16,²⁷ p21,²⁷ and epidermal growth factor receptor expression.^{28,29}

A better prognosis was observed for patients with OPC who underwent salvage surgery after disease progression compared with those who did not, regardless of p16 tumor status. To our knowledge, ours is the first study to report surgical salvage to be an independent predictor of survival for OPC within a prospective clinical trial. Our data are consistent with retrospective analyses that have observed improved survival rates after salvage surgery for locoregional persistent or recurrent disease.³⁰⁻³¹ Historically, salvage surgery was associated with significant morbidity and was perhaps inappropriate in the context of a short expected median survival rate. However, the improved survival rates observed herein argues in favor of strong consideration of the use of surgical salvage after locoregional progression of OPC. Our data could not address the effect of distant metastases resection on survival rates, as only a few patients with distant metastases (five of 181) underwent salvage surgery. Nevertheless, clinical trials should prospectively collect data on salvage surgery to ensure that survival differences between treatment arms are not explained by differences in salvage rates.

We note that the demographic and clinical characteristics that distinguish p16-positive and p16-negative patients at diagnosis (such as age, race, smoking status, tumor stage, and subsite)^{1,3} are also present among the subset of patients who subsequently experience disease progression. This underscores our current inability to identify

Table 4. Multivariable Analysis of Overall Survival in Oropharyngeal Cancer Patients With Disease Progression

Covariate	Limited to Patients With Known Pack-Years (n = 154; 100 events)			All Patients, With Imputed Pack-Years (n = 181; 123 events)		
	HR	95% CI	P	HR	95% CI	P
p16 status (positive v negative)	0.48	0.31 to 0.74	< .001	0.57	0.39 to 0.84	.005
T stage at enrollment (T4 v T2-T3)	1.61	1.06 to 2.45	.03	1.91	1.31 to 2.78	< .001
Progression type (distant v locoregional)	1.99	1.28 to 3.09	.002	1.70	1.13 to 2.54	.01
Salvage surgery (yes v no)	0.48	0.27 to 0.84	.01	0.56	0.34 to 0.92	.02
Pack-years (> 20 v ≤ 20)	1.57	1.02 to 2.44	.04	1.54	1.00 to 2.39	.05

Abbreviation: HR, hazard ratio from Cox proportional hazards model stratified by protocol.

patients who will experience disease progression from those who will not. Ideally, predictive biomarkers will be identified to distinguish patients at risk for disease progression versus those at low risk, for whom deintensification protocols are appropriate. Disease progression occurred for approximately 19% of RTOG 0129 and RTOG 0522 patients with low-risk OPC, and the majority of them (61.2%) had

locoregional disease progression. Data on the benefits of surgical salvage from our study will prove useful for patient counseling. In addition, our analysis of patterns of failure can inform clinical trial design for intermediate- and high-risk OPC patients. Although significant differences were not observed, trends toward increased risk of distant metastases in the intermediate-risk group were observed.

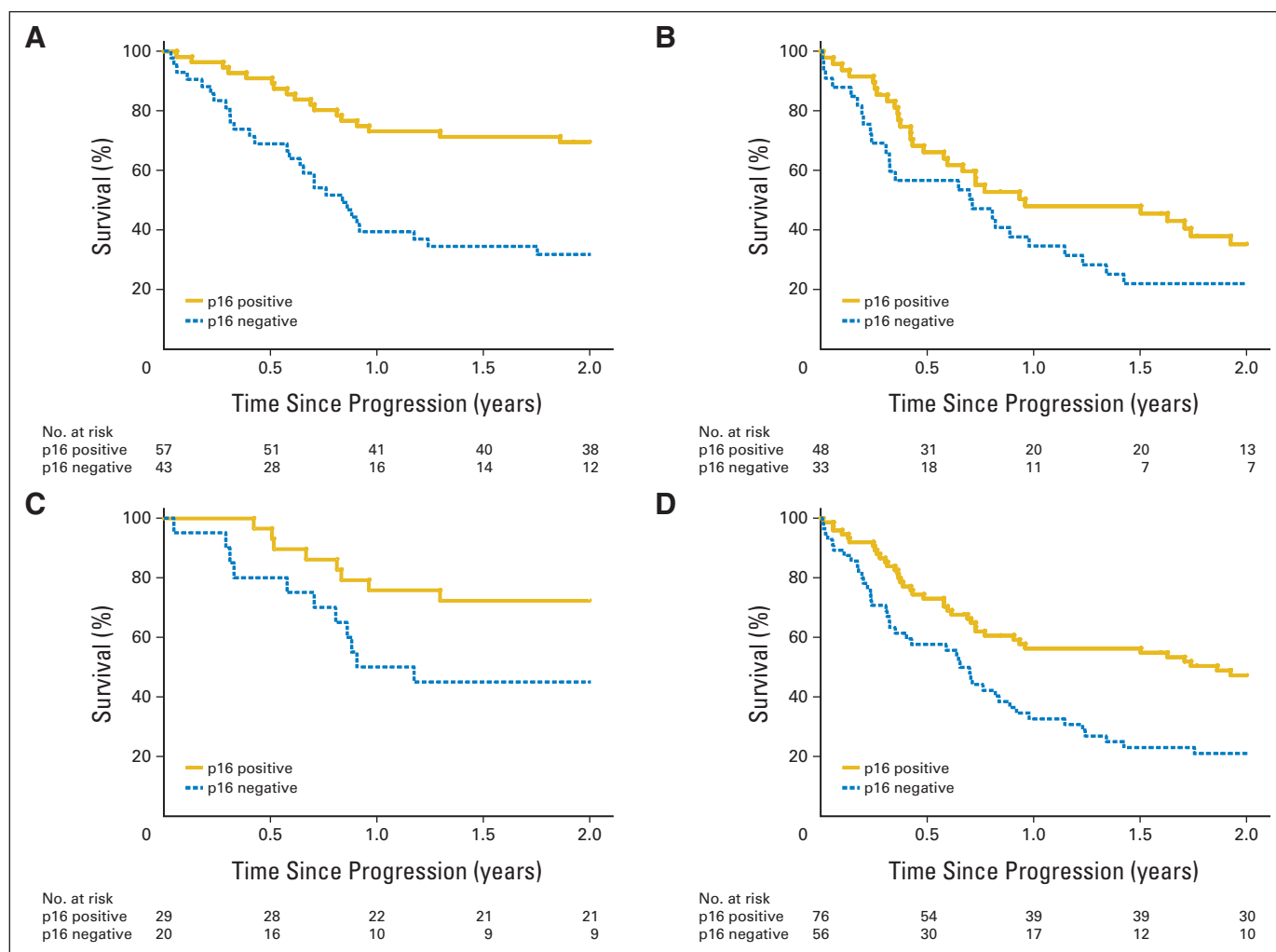


Fig 3. Kaplan-Meier estimates of overall survival after disease progression for patients with p16-positive and p16-negative oropharyngeal carcinoma (OPC) who had (A) locoregional progression, (B) distant metastases, (C) salvage surgery, and (D) no salvage surgery. Patients with p16-positive OPC had significantly better overall survival after disease progression than patients with p16-negative OPC in the subgroups that had locoregional failure ($P < .001$), distant metastases ($P = .04$), salvage surgery ($P = .004$), and no salvage surgery ($P = .003$).

The data from RTOG 0129 and RTOG 0522 dispel the notion that patterns of failure and time to disease progression differed by tumor p16 status.^{4,8,10-11} Instead, median time to disease progression and anatomic site involvement were similar. Time to disease progression serves as a surrogate end point for OS in head and neck cancer³²; however, further investigation will elucidate if this relationship differs by HPV status. The comparable time frame for disease progression and benefits of salvage surgery argue for similar post-treatment surveillance for p16-positive and p16-negative patients and close surveillance within the first 2 years of follow-up. The lungs were the most common site of distant metastases for both p16-positive and p16-negative OPC. Given this finding, p16 testing may be useful in differentiating lung metastases from second primary lung cancers.³³

Our data highlight previously unappreciated prognostic differences after disease progression between HPV-positive and HPV-negative OPC and underscore the need to identify biomarkers for risk of progression.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under

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GLOSSARY TERMS

p16: molecule that binds to cyclin-dependent kinase 4 and 6, thereby preventing their interaction with cyclin D. p16 (also known as p16^{INK4}) behaves as a negative regulator of proliferation and arrests cells in the G₀/G₁ phase of the cell cycle.

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Appendix

Table A1. Missing Data Analysis: Patient and Tumor Characteristics

Characteristic	p16 Tumor Status Unknown (n = 128)		p16 Tumor Status Known (n = 181)		P
	No. of Patients	%	No. of Patients	%	
Protocol					< .001*
ROG 0129	31	24.2	95	52.5	
ROG 0522	97	75.8	86	47.5	
Age at enrollment, years					.55†
Median	57		56		
Range	34-77		36-79		
Sex					.26*
Male	118	92.2	159	87.8	
Female	10	7.8	22	12.2	
Race					.51*
Asian	1	0.8	2	1.1	
Black or African American	19	14.8	21	11.6	
Native Hawaiian or other Pacific Islander	1	0.8	0	0.0	
White	107	83.6	157	86.7	
Unknown	0	0.0	1	0.6	
Zubrod PS at enrollment					.41*
0	81	63.3	105	58.0	
1	47	36.7	76	42.0	
Anemic at enrollment‡					1.00*
No	86	67.2	121	66.9	
Yes	42	32.8	60	33.1	
Smoking history, pack-years§	105		154		.77†
Median	28		23.75		
Range	0-85		0-104		
Primary site at enrollment					.45*
Oropharynx NOS	8	6.3	23	12.7	
Faucial arch	0	0.0	1	0.6	
Tonsillar fossa or tonsil	55	43.0	58	32.0	
Base of tongue	53	41.4	88	48.6	
Pharyngeal oropharynx	5	3.9	8	4.4	
Soft palate	7	5.5	3	1.7	
T stage at enrollment					.61†
T2	51	39.8	62	34.3	
T3	31	24.2	55	30.4	
T4	46	35.9	64	35.4	
N stage at enrollment					.54†
N0	7	5.5	9	5.0	
N1	11	8.6	17	9.4	
N2a	7	5.5	15	8.3	
N2b	37	28.9	65	35.9	
N2c	62	48.4	52	28.7	
N3	4	3.1	23	12.7	
AJCC stage at enrollment					.82*
III	10	7.8	12	6.6	
IV	118	92.2	169	93.4	
On-protocol RT dose, Gy					.94†
Median	70		70		
Range	4-74.4		0-75.9		

(continued on following page)

HPV, Oropharyngeal Carcinoma Progression, and Overall Survival

Table A1. Missing Data Analysis: Patient and Tumor Characteristics (continued)

Characteristic	p16 Tumor Status Unknown (n = 128)		p16 Tumor Status Known (n = 181)		P
	No. of Patients	%	No. of Patients	%	
On-protocol cisplatin cycles					.33†
0	1	0.8	3	1.7	
1	7	5.5	13	7.2	
2	109	85.2	136	75.1	
3	11	8.6	29	16.0	
First type of disease progression					.56*
Local	22	17.2	46	25.4	
Regional	37	28.9	46	25.4	
Local and regional	7	5.5	8	4.4	
Local and distant	7	5.5	6	3.3	
Regional and distant	3	2.3	3	1.7	
Local, regional, and distant	4	3.1	0	0.0	
Distant	48	37.5	72	39.8	
Salvage surgery within 6 weeks after progression					.60*
No	97	75.8	132	72.9	
Yes	31	24.2	49	27.1	

Abbreviations: AJCC, American Joint Committee on Cancer, 5th Edition (RTOG 0129) or 6th Edition (RTOG 0522); NOS, not otherwise specified; PS, performance status; RT, radiation therapy; RTOG, Radiation Therapy Oncology Group.

*Fisher's exact test. All non-white races were combined. Primary site was tested as tonsil or base of tongue versus others. Progression type was tested as distant (± locoregional) versus locoregional only.

†Wilcoxon rank-sum test.

‡Anemia is defined as a hemoglobin level of 13.5 g per deciliter or less for men and 12.5 g per deciliter or less for women.

§A pack-year is defined as the equivalent of smoking one pack of cigarettes per day for 1 year.

Table A2. Patient and Tumor Characteristics for Patients Who Did and Did Not Have Salvage Surgery

Characteristic	No Salvage Surgery (n = 132)		Salvage Surgery (n = 49)		P
	No. of Patients	%	No. of Patients	%	
Protocol					
RTOG 0129	69	52.3	26	53.1	
RTOG 0522	63	47.7	23	46.9	
Assigned treatment					
SFX and cisplatin	41	31.1	10	20.4	
AFX-C and cisplatin	57	43.2	23	46.9	
AFX-C, cisplatin, and cetuximab	34	25.8	16	32.7	
Age at enrollment, years					.05*
Mean	56.8		54.2		
SD	7.81		8.38		
Median	56.5		53		
Min-max	39-79		36-71		
Q1-Q3	52-63		49-60		
Sex					.32†
Male	114	86.4	45	91.8	
Female	18	13.6	4	8.2	
Race					.22†
Asian	1	0.8	1	2.0	
Black or African American	18	13.6	3	6.1	
White	112	84.8	45	91.8	
Unknown	1	0.8	0	0.0	
Zubrod PS at enrollment					.23*
0	73	55.3	32	65.3	
1	59	44.7	17	34.7	
Hemoglobin at enrollment, g/dL					.26*
Mean	13.8		14.1		
SD	1.77		1.43		
Median	14.1		14.2		
Min-max	8.2-18.6		10-16.8		
Q1-Q3	12.7-14.95		13.4-15		
Anemic at enrollment					.25†
No	85	64.4	36	73.5	
Yes	47	35.6	13	26.5	
Smoking history, pack-years‡	115		39		.26*
Mean	29.0		24.1		
SD	24.81		24.52		
Median	26.25		15		
Min-max	0-96		0-104		
Q1-Q3	5-43.75		1.8-46.25		
Primary site at enrollment					.84†
Oropharynx, NOS	17	12.9	6	12.2	
Faucial arch	1	0.8	0	0.0	
Tonsillar fossa or tonsil	43	32.6	15	30.6	
Base of tongue	63	47.7	25	51.0	
Pharyngeal oropharynx	5	3.8	3	6.1	
Soft palate	3	2.3	0	0.0	
p16 status					.85*
Negative	56	42.4	20	40.8	
Positive	76	57.6	29	59.2	
T stage at enrollment					.37*
T2	43	32.6	19	38.8	
T3	40	30.3	15	30.6	
T4	49	37.1	15	30.6	

(continued on following page)

HPV, Oropharyngeal Carcinoma Progression, and Overall Survival

Table A2. Patient and Tumor Characteristics for Patients Who Did and Did Not Have Salvage Surgery (continued)

Characteristic	No Salvage Surgery (n = 132)		Salvage Surgery (n = 49)		P
	No. of Patients	%	No. of Patients	%	
N stage at enrollment					.88*
N0	6	4.5	3	6.1	
N1	12	9.1	5	10.2	
N2a	11	8.3	4	8.2	
N2b	48	36.4	17	34.7	
N2c	39	29.5	13	26.5	
N3	16	12.1	7	14.3	
AJCC stage at enrollment					.41*
III	10	7.6	2	4.1	
IV	122	92.4	47	95.9	
On-protocol RT dose, Gy					.88*
Mean	70.6		68.7		
SD	1.25		10.28		
Median	70		70		
Min-max	68-75.9		0-72.76		
Q1-Q3	70-71.68		70-72		
On-protocol cisplatin cycles					.37*
0	2	1.5	1	2.0	
1	10	7.6	3	6.1	
2	96	72.7	40	81.6	
3	24	18.2	5	10.2	

Abbreviations: AJCC, American Joint Committee on Cancer, 5th edition (for RTOG 0129) or 6th Edition (for RTOG 0522); AFX-C, accelerated fractionation by concomitant boost radiotherapy; BOT, base of tongue; min, minimum; max, maximum; NOS, not otherwise specified; PS, performance status; Q1, first quartile; Q3, third quartile; RT, radiation therapy; RTOG, Radiation Therapy Oncology Group; SD, standard deviation; SFX, standard fractionation radiotherapy.

*Wilcoxon rank-sum test.

†Pearson χ^2 test. All non-white races were combined. Primary site is tested as tonsil or BOT versus others.

‡A pack-year is defined as the equivalent of smoking one pack of cigarettes a day for 1 year.

Table A3. Multivariable Analysis of Overall Survival in Oropharyngeal Cancer Patients With Disease Progression

Covariate	Limited to Patients With Known Pack-Years (n = 154; 100 events)			All Patients, With Imputed Pack-Years (n = 181; 123 events)		
	HR	95% CI	P	HR	95% CI	P
p16 status (positive v negative)	0.48	0.31 to 0.74	< .001	0.55	0.37 to 0.82	.003
T stage at enrollment (T4 v T2-T3)	1.61	1.06 to 2.46	.03	1.91	1.31 to 2.79	< .001
Progression type (distant v locoregional)	1.96	1.24 to 3.10	.004	1.61	1.06 to 2.43	.02
Salvage surgery (yes v no)	0.48	0.27 to 0.84	.01	0.56	0.34 to 0.92	.02
Pack-years (> 20 v ≤ 20)	1.57	1.01 to 2.44	.05	1.52	0.98 to 2.36	.06
Age at enrollment (> 50 v ≤ 50)	0.97	0.56 to 1.68	.92	1.07	0.66 to 1.74	.77
Race (non-white v white)	1.01	0.56 to 1.84	.97	0.95	0.56 to 1.64	.87
N stage at enrollment (N2b-N3 v N0-N2a)	1.12	0.67 to 1.86	.67	1.28	0.80 to 2.04	.30

Abbreviation: HR, hazard ratio from Cox proportional hazards model stratified by protocol.

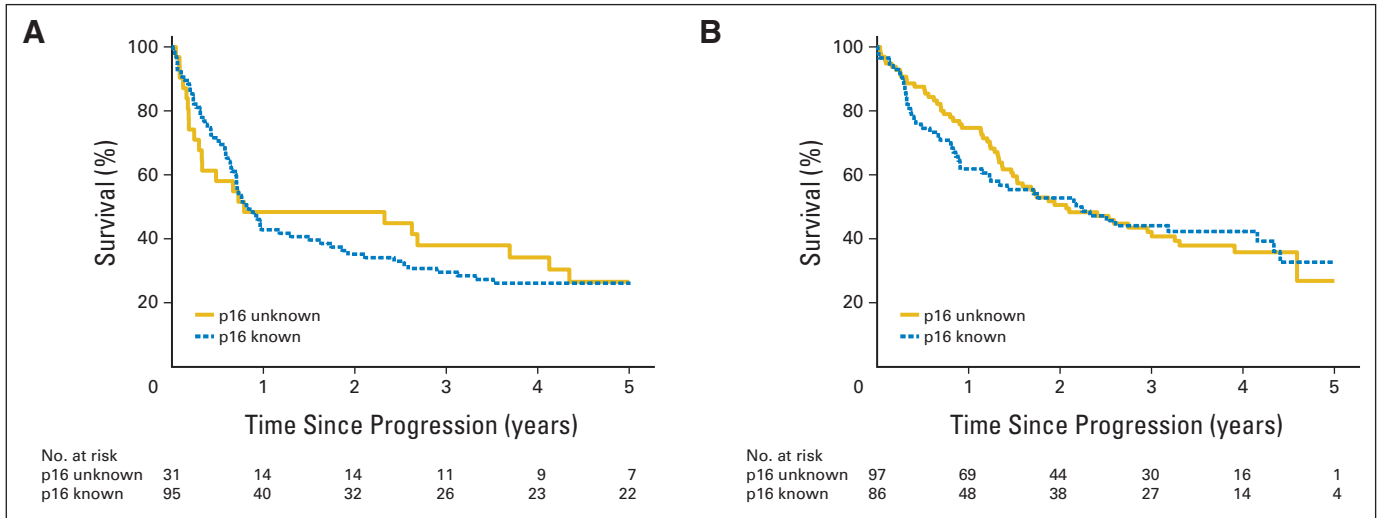


Fig A1. Kaplan-Meier estimates of survival after disease progression for patients with known and unknown p16 tumor status in (A) Radiation Therapy Oncology Group (RTOG) 0129 and (B) RTOG 0522. There are no statistically significant differences in survival after disease progression between patients with known and unknown p16 tumor status in RTOG 0129 (log-rank test, $P = .88$) or RTOG 0522 (log-rank test, $P = .85$).