



## Conditional Survival Among Patients With Oropharyngeal Cancer Treated With Radiation Therapy and Alive Without Recurrence 5 Years After Diagnosis

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### Abstract

**BACKGROUND:** Risk of recurrence among patients with oropharyngeal cancer (OPC) who survive 5 years is low. The goal of this study was to assess long-term survival of patients with OPC alive without recurrence 5 years after diagnosis.

**METHODS:** This study included newly diagnosed patients with OPC, who had been treated with radiation and were alive without recurrence 5 years after diagnosis. Overall survival (OS) probabilities beyond 5 years were estimated using the Kaplan-Meier method. Factors associated with OS were determined using Bayesian piecewise exponential survival regression. Standardized

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#### AUTHOR CONTRIBUTIONS

**Adam S. Garden:** Study concept and design, data acquisition, statistical analysis, and manuscript writing. **G. Brandon Gunn:** Data acquisition. **Jack Phan:** Data acquisition. **Steven J. Frank:** Data acquisition. **William H. Morrison:** Data acquisition. **David I. Rosenthal:** Data acquisition. **Erich M. Sturgis:** Data acquisition. **Kristina R. Dahlstrom:** Statistical analysis and manuscript writing. **Juhee Song:** Statistical analysis. **Peter F. Thall:** Statistical analysis, and manuscript writing. All authors: Data interpretation and manuscript review and editing.

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mortality ratios for all-cause death were estimated controlling for study year, age, and sex in the US general population.

**RESULTS:** Among 1699 patients, the additional 2-year, 5-year, and 10-year OS probabilities were 94%, 83%, and 63%, respectively, and were lower than those in the general population. Patients who were older, were current or former smokers, had other than tonsil or base of tongue tumors, or had T4 tumors had a higher risk of death. Patients who had base of tongue tumors and had received intensity-modulated radiation therapy (IMRT) or lower-radiation doses had a lower risk of death. Standardized mortality ratios were higher among current and heavy smokers and lower among recipients of IMRT and lower radiation doses.

**CONCLUSIONS:** In this large cohort, long-term survival among patients with OPC was good but lower than predicted for the general population. Patients treated with IMRT and those with less tobacco exposure had better outcomes.

### Keywords

conditional survival; head and neck neoplasms; oropharyngeal cancer; radiation therapy; standardized mortality ratios

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## INTRODUCTION

Patients with head and neck cancers (HNCs) commonly present with local, regionally advanced disease. Recurrence rates depend on primary tumor site and stage; regardless, the majority of recurrences manifest within 2 years after treatment, and the likelihood of recurrence after 5 years is <2%.<sup>1</sup>

Patients with human papillomavirus (HPV)–related oropharyngeal cancer (OPC), including p16-positive tumors, have higher survival rates than patients with HPV-unrelated disease<sup>2–4</sup>; however, the Radiation Therapy Oncology Group (RTOG) has demonstrated that p16-positive and p16-negative patients have similar time to recurrence, with >80% occurring within 2 years after therapy.<sup>5</sup> Several groups have described late recurrences among patients with HPV-related disease, but these events are uncommon.<sup>6</sup> Thus, the probability of recurrence beyond 5 years after completion of therapy is very low.

In a recent randomized trial of patients with HPV-related OPC, 5-year overall survival (OS) was approximately 80%.<sup>7</sup> This has led investigators to focus on reducing treatment toxicity, and though a laudable goal in and of itself, long-term results from past RTOG studies have hinted that toxicity reduction may also improve long-term survival.<sup>8,9</sup>

Conditional survival, the probability of additional survival given that a patient has already survived a specified amount of time,<sup>10</sup> is one metric for understanding the long-term prognosis of cancer survivors who have remained recurrence-free for many years after treatment. It can be reported in absolute terms with Kaplan-Meier techniques that define survival rates from a time point after diagnosis (eg, completion of treatment) in a patient who has survived to that new time point, and in relative terms, comparing survival with that of an age- and period-adjusted normal population.

Recognizing that the majority of patients with OPC survive at least 5 years ( $\approx 80\%$ ) and have a low probability of recurrence, we sought to identify factors that influenced long-term survival in a cohort of patients with OPC treated with radiation who survived recurrence-free for at least 5 years after diagnosis.

## MATERIALS AND METHODS

The study was a retrospective database review approved by the institutional review board of The University of Texas MD Anderson Cancer Center. A database maintained in the Department of Radiation Oncology was searched using the following criteria: 1) incident squamous cell OPC with radiation treatment to the oropharynx, 2) diagnosis during 1980–2012, 3) survival after diagnosis at least 5 years, 4) gross disease at the primary site and/or neck at the time of treatment start (patients with unknown primary site were excluded), and 5) no cancer event during the 5 years after diagnosis. The majority of patients who presented to the institution during the study period were treated with radiation; patients who were not irradiated at the institution ( $<15\%$ ) or were treated with primary surgery ( $<2\%$ ) were not included in the analysis.

### Statistical Analysis

Patient characteristics were summarized using the median and interquartile range (IQR) for continuous variables and counts and percentages for categorical variables. OS time was defined as the time from 5 years after diagnosis to death. Vital status (date of death, last follow-up, and time to progression) was determined through review of medical records that included information collected through periodic review of the Social Security Death Index, the State Bureau of Vital Statistics, and the State Cancer Registry. Because of the difficulty of distinguishing between second primary tumors and recurrence in head and neck mucosal sites, all occurrences of squamous malignancies in a head and neck site and all metastatic squamous cell cancer were considered recurrences.

The Kaplan-Meier method was used to estimate OS probabilities beyond 5 years. Bayesian piecewise exponential survival regression models<sup>11</sup> were fit to assess the effects of patient covariates on OS time. The covariates included age, sex, smoking status at diagnosis, primary tumor site, T category, N category, radiation therapy dose, and receipt of intensity-modulated radiation therapy (IMRT), neck dissection, or chemotherapy. To evaluate possible interactions between T category and radiation dose, a second model also included 2 indicator variables (T1-T2 and radiation dose 20–66 Gy vs not; T2-T3 and radiation dose  $>67$  vs not). Neither of the interaction terms were statistically significant and were not included in the final model. To avoid collinearity and an unstable fitted model, period of diagnosis (1980–1989, 1990–1999, 2000–2013) and pack-years of smoking were not included because 1) the period of diagnosis was highly correlated with IMRT (no patient received IMRT prior to 2000), and 2) pack-years was highly correlated with smoking status and was missing for 63 patients. Each model assumed a noninformative gamma prior for the hazard parameters and noninformative normal priors for the covariate coefficients. Separate models with 1 to 10 subintervals were fit, and the model with the smallest deviance information criterion,<sup>12</sup> which had 7 subintervals, was selected (additional details provided in Supporting

Information). A graphical user interface (GUI) to compute posterior estimates of OS based on individual patient covariates was constructed using the fitted survival model (<https://biostatistics.mdanderson.org/shinyapps/BayesianSurvival/>).

Standardized mortality ratios (SMRs) for all-cause death<sup>13–15</sup> were estimated for specified subgroups, controlling for study year, age, and sex in the US general population.<sup>16,17</sup> CIs and significance tests for SMRs were calculated using a normal approximation. The indirect standardization method, which uses the stratum-specific (study year, age, and sex) rate estimates in the reference population to compute the expected number of events in the study population, was used. The Ederer II method<sup>18</sup> was used to calculate adjusted expected survival curves from US mortality data, and the Kaplan-Meier method<sup>19</sup> was used to estimate 2-, 5-, and 10-year unadjusted OS probabilities for the study population. SAS 9.4 (SAS, Inc) was used for all statistical computations.

## RESULTS

Of 3100 patients with OPC, 1699 met the inclusion criteria (Supporting Fig. 1). Patient characteristics are summarized in Table 1. The median age was 60 years (IQR, 55–68 years). HPV (by in situ hybridization) and/or p16 immunohistochemistry testing was only available for patients diagnosed after 1999. Of 477 patients, 429 (90%) had an HPV-related tumor. The median radiation dose was 70 Gy (IQR, 66–70.5 Gy).

A total of 308 patients (18%) had a cancer event after time zero (ie, after having survived 5 years from diagnosis; Table 1). Eighty-five patients developed an HNC recurrence: 45 solely in a head and neck site, 5 with isolated nodal recurrences, and 35 with distant metastases. Twelve of the 35 patients with distant metastases had a known history of a second primary (non-head and neck) squamous cancer, a potential source of the metastases in some cases. Patients who suffered a cancer event were more likely to have ever smoked than those who did not (67% vs 53%;  $P < .001$ ).

A total of 496 patients (29%) died during the study follow-up, including 197 (64%) with a cancer event. The median follow-up time from 5 years after diagnosis for all patients was 6.7 years (95% CI, 6.4–7.0; ie, 11.7 years from diagnosis). Figure 1 shows Kaplan-Meier estimates of OS for all patients along with age- and sex-adjusted expected survival probabilities based on US mortality data for 1985, 1995, and 2005. Patients had significantly worse survival over time compared with the general population. The unadjusted 2-, 5-, and 10-year survival probabilities were 94%, 83%, and 63%, respectively, for the full study population (Table 2).

Figure 2 shows Kaplan-Meier estimates of OS by period of diagnosis, pack-years of smoking, IMRT, radiation dose, and chemotherapy along with corresponding expected survival probabilities from the general population. Although patients had worse survival than the general population regardless of the decade of diagnosis, survival improved over time; 67% of those diagnosed from 2000 through 2013 survived at least 10 years from time zero, compared with 58% from 1990–1999 and 54% from 1980–1989 (Fig. 2A and Table 2).

Heavy smokers had significantly worse survival than light/never smokers (10-year rate: 50% for >10 vs 75% for 10 pack-years), and both groups had poorer survival than the general population (Fig. 2B and Table 2). Only patients diagnosed after 2000 received IMRT and had better survival than those who did not receive IMRT (Fig. 2C and Table 2). Lower radiation doses were associated with improved survival (10-year rate: 72% for 66 Gy vs 58% for >70 Gy, although some overlap between groups was observed; Fig. 2D and Table 2). Patients who received concurrent chemotherapy had the lowest 10-year rate, and patients who received adjuvant chemotherapy had the highest, although significant overlap was observed between groups (Fig. 2E and Table 2).

The fitted Bayesian piecewise exponential model is summarized in Table 3, including each covariate's posterior mean hazard ratio, 95% Bayesian credible interval, and posterior probability of a beneficial effect (PBE) on OS for a larger value of the covariate. For example, PBE = 0.05 indicates that the covariate is associated with shorter survival, whereas PBE = 0.95 indicates that there is a 0.95 probability of longer survival time for larger values of the covariate. Older age, current/former smoking, other than tonsil or base of tongue tumor site, and T4 category were all independently associated with increased risk of death (lower PBE). Base of tongue tumor site, use of IMRT, and lower radiation dose (66 Gy vs >70 Gy) were associated with lower risk of death (larger PBE).

For all subgroups except HPV-negative status, the SMRs were significantly larger than 1 compared with the general population, indicating a significantly higher mortality rate among patients (Table 4). Although the SMR for the HPV-negative group was >1, this was not statistically significant. Overall, mortality was 4 times higher among patients than the general population. Notably, the SMR for patients diagnosed in earlier periods was higher than for those more recently diagnosed (5.6 for 1980–1989 vs 2.9 for 2000–2013; Table 4). Current and high intensity of smoking were both associated with higher SMRs (7.4 for current smoker vs 2.8 for never smoker; 5.4 for >10 vs 2.7 for 10 pack-years). The SMR for patients receiving IMRT was 2.3, compared with 5.2 for those not receiving IMRT, and was lowest for patients who received a radiation dose in the lowest tertile (2.4 for 66 Gy vs 5.0 for >70 Gy). We believe that the nonsignificant result for HPV-negative patients is due to insufficient statistical power caused by the small sample size (N = 48).

## DISCUSSION

Among 1699 patients with newly diagnosed OPC treated with definitive radiation therapy (with or without chemotherapy) and alive without recurrence 5 years after diagnosis, the likelihood of living an additional 5 years was >80% and the likelihood of living an additional 10 years was 60%.

Although long-term survival rates for this population were good, they were lower than those of the general population. Based on this finding, we offer the following interpretations: 1) although patients with OPC who survive at least 5 years after diagnosis have very good long-term outcomes with low recurrence rate, their mortality rate nonetheless remains higher than that of the general population due to their index cancer; 2) unaccounted-for effects of

treatment contribute to mortality; or 3) our population of patients was inherently at greater risk for death.

Regarding our first interpretation, although several authors have cautioned that for HPV-related OPC particularly, late recurrences can occur,<sup>6</sup> the likelihood is very low.<sup>1-5</sup> Only 5% of our patients had an HNC event in the time interval of interest. In many patients, it was difficult to distinguish between recurrent disease and a second primary tumor. In particular, hematogenous recurrences accounted for <2% of cancer events overall and approximately 40% of the HNC events, and we speculate that some hematogenous recurrences were related to second primary cancers. Finally, these few HNC events, even if they had all led to death (which they did not), would have accounted for <25% of the deaths observed in addition to the number of deaths expected.

Regarding our second interpretation, as more patients survive many years following treatment, more data are becoming available from which to gain insight into the long-term sequelae of high-dose radiation therapy, which is often combined with chemotherapy.<sup>20-22</sup> Our group and others have described chronic radiation-associated dysphagia and late cranial neuropathies contributing to dysphagia.<sup>22-26</sup> These late dysphagia events, particularly in older patients,<sup>27</sup> can lead to aspiration, which either directly or indirectly can lead to a mortal event.<sup>28,29</sup> Based on our results, we speculate that radiation sequelae contribute to mortality. Increased risk of death with higher T category is commonly attributed to higher risk of recurrence. However, the vast majority of our patients remained recurrence-free. Although it is possible that the T category was a surrogate for a larger volume of pharynx receiving high doses of radiation, we found no evidence of a joint effect of T category and radiation dose. Perhaps a more plausible explanation is that T4 tumors frequently present with functional compromise that does not completely resolve following treatment.

An important finding about the long-term sequelae of aggressive therapy is that IMRT, specifically designed to avoid structures within the head and neck that do not need radiation, resulted in 5-year and 10-year OS rates >10% higher than in patients treated with non-IMRT techniques. SEER-Medicare analyses from our group have demonstrated both improved cause-specific survival rates and lower gastrostomy rates in patients with HNC treated with IMRT.<sup>30,31</sup> Although the improvement in cause-specific survival was likely due to better target coverage, both analyses suggested that toxicity reduction with the use of IMRT was also important.

We also found that chemotherapy had only a weak negative impact on long-term outcomes. In the RTOG 91-11 report, the seminal RTOG trial testing nonsurgical approaches for advanced laryngeal cancer, deaths not attributed to cancer or obvious toxic effects were more frequent in patients treated concurrently with chemotherapy and radiation.<sup>8</sup> The authors believed that this could have been secondary to fatal treatment-related episodes not identified by the monitoring techniques used. We did not reproduce this finding; in our study, patients who received concurrent chemotherapy or radiation alone had similar survival rates.

Our third interpretation relates to an increased risk of death within the study population irrespective of the index disease and therapy. The observed differences in survival based on smoking history support this. Ten-year survival rates were 75% for patients with a smoking history of  $\leq 10$  pack-years compared with 50% for those with  $>10$  pack-years, and the SMR in those who smoked  $>10$  pack-years was nearly double the SMR in those who smoked less or not at all. The prevalence of smoking among adults in the United States in 2005 was 21%,<sup>32</sup> whereas 22% of our patients were current and 34% were former smokers, suggesting that our population had a greater exposure to cigarettes that, in part, led to a higher SMR. Additionally, the lower prevalence of smoking among patients diagnosed during 2000–2013 (52%) compared with those diagnosed prior to 2000 (69% for 1980–1989 and 64% for 1990–1999) could have contributed to improved survival over time. However, despite clear correlation of poorer outcome with smoking, our never-smoker subgroup had an SMR = 2.8.

One limitation of our study was that cause of death was not captured, allowing only speculation on the causes of lower long-term survival rates in patients than the general population. As mentioned, late cranial neuropathies and dysphagia with associated aspiration are clear effects of therapy. Conversely, an increased risk of stroke among patients who undergo irradiation of the neck has been observed,<sup>33–35</sup> yet carotid ischemic events are a common cause of morbidity and mortality in the general population, so attribution of our observation to radiation, particularly in the absence of pretreatment and posttreatment carotid imaging, is a challenge. Additional potentially life-threatening sequelae of irradiation of the neck, including baroreceptor dysfunction,<sup>36</sup> are just starting to be recognized. Ultimately, the hypothesized negative impact on conditional survival of having OPC treated with definitive radiation is multifactorial.

Another limitation was the lack of known HPV status for the majority of patients. HPV prevalence in OPC tumors has increased dramatically over the past few decades in the United States, and HPV positivity is a strong independent predictor of better survival.<sup>2,3</sup> However, this is mainly due to better disease control in the first few years from treatment. It is unlikely that tumor HPV status directly impacts conditional survival, though the underlying demographics of patients with HPV-related tumors (younger age, less comorbidity, less tobacco exposure) may have some impact on our findings.

Although our finding of improved survival among patients with OPC in the more recent time period could be ascribed to stage migration (ie, patients more recently diagnosed being assigned a higher stage due to advancements in technology allowing detection of more disease), this is unlikely. Under the assumption that a patient does not die of disease, stage can only theoretically be impactful if 1) it influenced the intensity of treatment, and survival is impacted by treatment intensity (ie, more intense correlates and late toxicity that impacts survival); or 2) the original stage had not only more extensive disease but that disease caused damage that influenced late survival (eg, more extensive disease caused tongue impairment that led to the patient aspirating). In conclusion, the overall 10-year conditional survival rate (15 years from diagnosis) was 63% among 1699 patients with OPC treated with radiation and cancer-free 5 years after diagnosis. Patients treated with IMRT and those with less tobacco exposure had better outcomes but still had poorer outcomes when compared with the general population.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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### CONFLICT OF INTEREST DISCLOSURES

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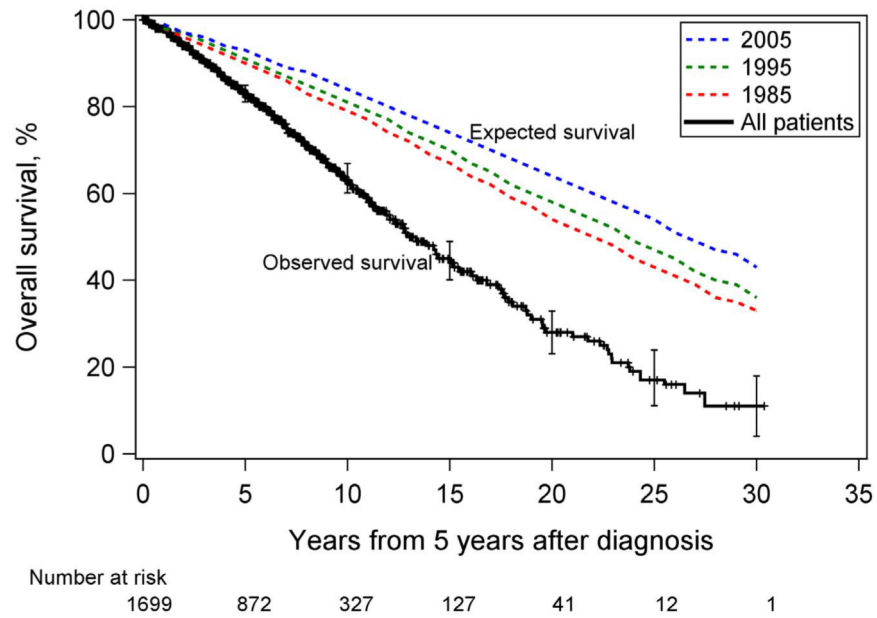
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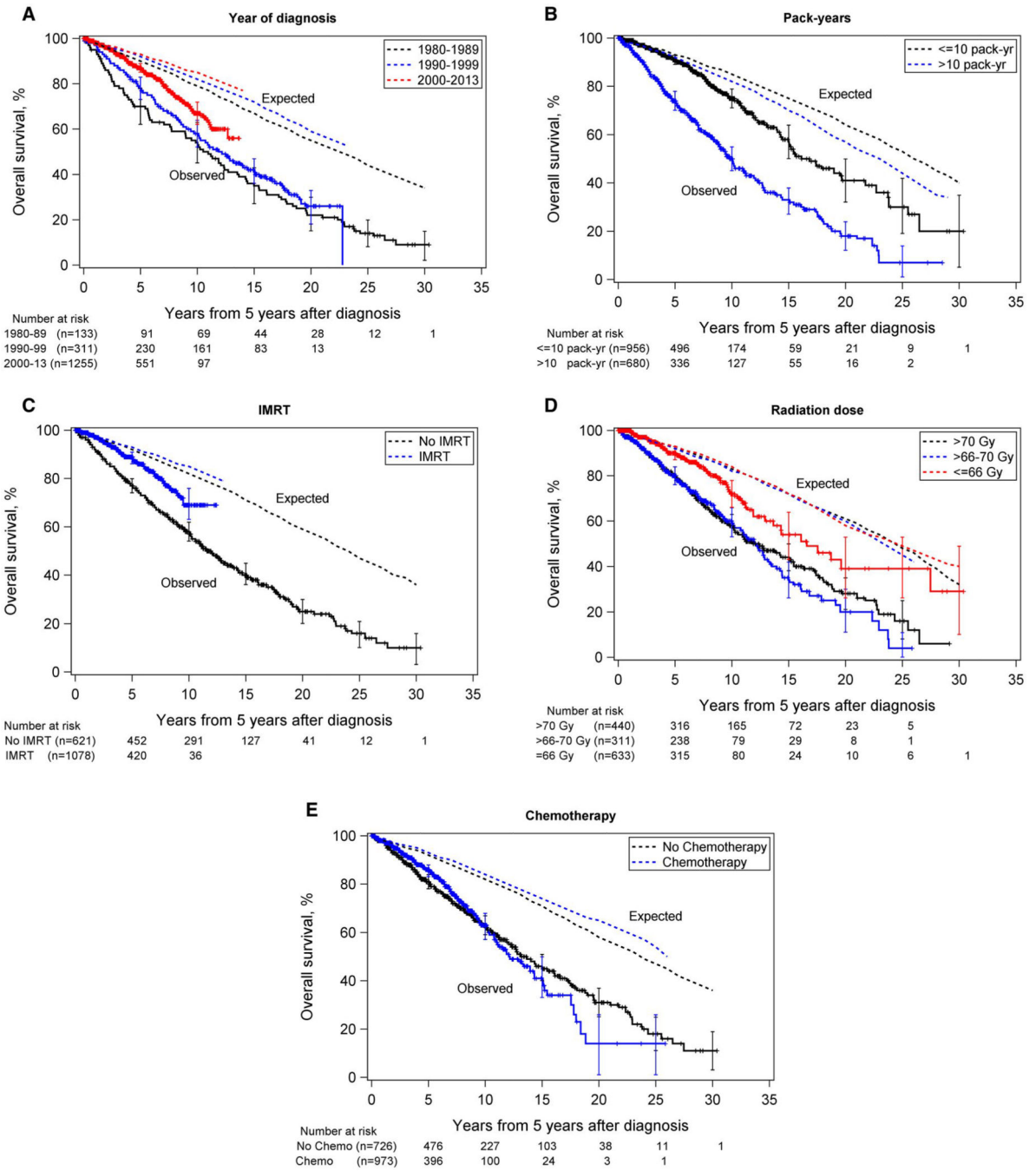


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**Figure 1.** Overall survival of patients with oropharyngeal cancer who had already survived 5 years after diagnosis. Age- and sex-adjusted expected survival curves for the general US population for 1985, 1995, and 2005 are also shown. Vertical bars are 95% CIs. The time scale begins at 5 years after diagnosis.



**Figure 2.** Overall survival of patients with oropharyngeal cancer who had already survived 5 years after diagnosis by (A) year of diagnosis, (B) pack-years of smoking (including never smokers), (C) receipt of intensity-modulated radiation therapy (IMRT), (D) radiation dose, and (E) receipt of chemotherapy. Solid lines represent patients; dotted lines represent the corresponding study year-, age-, and sex-adjusted expected survival rates for the general US population. Vertical bars are 95% CIs. The time scale begins at 5 years after diagnosis.

**TABLE 1.**

Demographic and Clinical Characteristics of Patients With Oropharyngeal Cancer Who Survived at Least 5 Years After Diagnosis

Characteristic	No. of Patients (%)
Age at diagnosis, median (IQR), y	60 (55–68)
Radiation dose, median (IQR), Gy	70 (66–70.5)
Sex	
Male	1407 (82.8)
Female	292 (17.2)
Period of diagnosis	
1980–1989	133 (7.8)
1990–1999	311 (18.3)
2000–2013	1255 (73.9)
Smoking status	
Never	744 (44.2)
Former	571 (33.9)
Current	370 (22.0)
Missing	14
Smoking, pack-years	
10	956 (58.4)
>10	680 (41.6)
Missing	63
Site	
Tonsil	773 (45.5)
Base of tongue	821 (48.3)
Other	105 (6.2)
HPV status	
Negative	48 (10.1)
Positive	429 (89.9)
Missing	1222
T category	
T1	523 (30.8)
T2	639 (37.6)
T3	353 (20.8)
T4	183 (10.8)
Missing	1
N category (AJCC 7th ed.)	
N0	218 (12.9)
N1	330 (19.4)
N2	1045 (61.5)
N3	105 (6.2)
Missing	1

Characteristic	No. of Patients (%)
Neck dissection	
No	1306 (76.9)
Yes	393 (23.1)
IMRT	
No	621 (36.6)
Yes	1078 (63.4)
Fractionation	
Conventional	1164 (68.7)
Concomitant boost	456 (26.9)
Other	75 (4.4)
Missing	4
Radiation dose, Gy	
>70	440 (26.0)
>66–70	622 (36.7)
66	633 (37.3)
Missing	4
Chemotherapy	
None	726 (42.7)
Adjuvant only	266 (15.7)
Concurrent only	485 (28.5)
Both	222 (13.1)
Recurrence <sup>a</sup>	
None	1614 (95.0)
Local	53 (3.1)
Regional	9 (0.5)
Distant	35 (2.1)
Second primary tumor	
No	1408 (84.5)
Yes	258 (15.5)
Missing	33

Abbreviations: AJCC, American Joint Committee on Cancer; HPV, human papillomavirus; IMRT, intensity-modulated radiation therapy; IQR, interquartile range.

<sup>a</sup>Groups not mutually exclusive.

**TABLE 2.**

Kaplan-Meier Estimates of 2-, 5-, and 10-Year Unadjusted Survival Probabilities of Patients With Oropharyngeal Cancer Who Survived at Least 5 Years After Diagnosis

Subgroup	Survival Probability (95% CI)		
	2 y	5 y	10 y
Full study population	0.94 (0.93–0.95)	0.83 (0.81–0.85)	0.63 (0.60–0.67)
Age at diagnosis, y			
<55	0.97 (0.94–0.98)	0.91 (0.87–0.93)	0.80 (0.74–0.84)
55	0.93 (0.92–0.95)	0.81 (0.78–0.83)	0.57 (0.53–0.61)
Period of diagnosis			
2000–2013	0.96 (0.95–0.97)	0.87 (0.85–0.89)	0.67 (0.62–0.71)
1990–1999	0.92 (0.88–0.94)	0.78 (0.73–0.82)	0.58 (0.52–0.63)
1980–1989	0.86 (0.79–0.91)	0.70 (0.62–0.77)	0.54 (0.45–0.62)
Sex			
Male	0.94 (0.93–0.96)	0.84 (0.82–0.86)	0.64 (0.60–0.68)
Female	0.93 (0.90–0.96)	0.80 (0.75–0.85)	0.60 (0.53–0.67)
Smoking status			
Never	0.97 (0.95–0.98)	0.92 (0.89–0.94)	0.76 (0.71–0.80)
Former	0.95 (0.93–0.97)	0.81 (0.77–0.85)	0.61 (0.55–0.67)
Current	0.88 (0.85–0.91)	0.71 (0.66–0.76)	0.47 (0.41–0.54)
Smoking, pack-y			
>10	0.91 (0.88–0.93)	0.74 (0.70–0.77)	0.50 (0.45–0.55)
10	0.97 (0.95–0.98)	0.91 (0.89–0.93)	0.75 (0.71–0.79)
Site			
Tonsil	0.94 (0.92–0.95)	0.84 (0.80–0.86)	0.64 (0.59–0.68)
Base of tongue	0.95 (0.94–0.97)	0.86 (0.83–0.89)	0.69 (0.64–0.73)
Other	0.87 (0.78–0.92)	0.63 (0.52–0.72)	0.34 (0.24–0.45)
T category			
T1	0.96 (0.94–0.98)	0.89 (0.85–0.92)	0.71 (0.65–0.77)
T2	0.94 (0.92–0.96)	0.85 (0.81–0.88)	0.69 (0.64–0.74)
T3	0.93 (0.90–0.96)	0.79 (0.74–0.83)	0.53 (0.46–0.60)
T4	0.91 (0.86–0.95)	0.72 (0.63–0.79)	0.43 (0.32–0.53)
N category (AJCC 7th ed.)			
N0	0.88 (0.83–0.92)	0.71 (0.64–0.77)	0.51 (0.43–0.58)
N1	0.94 (0.90–0.96)	0.84 (0.79–0.88)	0.64 (0.57–0.71)
N2	0.96 (0.95–0.97)	0.87 (0.84–0.89)	0.67 (0.62–0.71)
N3	0.88 (0.79–0.93)	0.75 (0.65–0.83)	0.56 (0.44–0.67)
Neck dissection			
No	0.94 (0.92–0.95)	0.82 (0.80–0.85)	0.62 (0.58–0.65)
Yes	0.95 (0.92–0.97)	0.86 (0.82–0.89)	0.69 (0.63–0.75)
IMRT			
No	0.91 (0.88–0.93)	0.77 (0.73–0.80)	0.58 (0.53–0.61)

Subgroup	Survival Probability (95% CI)		
	2 y	5 y	10 y
Yes	0.97 (0.95–0.98)	0.89 (0.86–0.91)	0.69 (0.62–0.75)
Radiation dose, Gy			
>70	0.93 (0.90–0.95)	0.80 (0.76–0.83)	0.58 (0.53–0.63)
>66–70	0.92 (0.90–0.94)	0.80 (0.75–0.83)	0.60 (0.53–0.65)
66	0.97 (0.95–0.98)	0.90 (0.87–0.92)	0.72 (0.65–0.77)
Chemotherapy			
None	0.93 (0.91–0.95)	0.81 (0.78–0.84)	0.63 (0.59–0.67)
Adjuvant only	0.96 (0.92–0.98)	0.89 (0.84–0.93)	0.71 (0.62–0.79)
Concurrent only	0.94 (0.91–0.96)	0.83 (0.79–0.87)	0.58 (0.50–0.65)
Both	0.97 (0.93–0.98)	0.88 (0.81–0.93)	0.61 (0.39–0.77)

Abbreviations: AJCC, American Joint Committee on Cancer; IMRT, intensity-modulated radiation therapy.

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**TABLE 3.**

Factors Associated With Overall Survival of Patients With Oropharyngeal Cancer Who Survived at Least 5 Years After Diagnosis

Subgroup	Posterior Mean HR (95% CRI)	Posterior Probability of Longer Overall Survival
Age (per 1-year increase)	1.080 (1.069–1.092)	0.0000
Sex		
Male	1.000	
Female	0.932 (0.734–1.161)	0.7422
Smoking status		
Never	1.000	
Former	1.276 (1.002–1.597)	0.0238
Current	2.158 (1.701–2.713)	0.0000
Site		
Tonsil	1.000	
Base of tongue	0.747 (0.606–0.908)	0.9982
Other	1.337 (0.986–1.764)	0.0303
T category		
T1	1.000	
T2	1.024 (0.765–1.343)	0.4630
T3	1.224 (0.880–1.653)	0.1195
T4	1.482 (1.008–2.094)	0.0225
N category (AJCC 7th ed.)		
N0	1.000	
N1	1.056 (0.787–1.388)	0.3812
N2	1.009 (0.775–1.298)	0.5026
N3	1.259 (0.834–1.799)	0.1411
Neck dissection		
No	1.000	
Yes	0.990 (0.778–1.235)	0.5539
IMRT		
No	1.000	
Yes	0.776 (0.588–1.004)	0.9735
Radiation dose, Gy		
>70	1.000	
>66–70	1.067 (0.851–1.320)	0.3004
66	0.718 (0.522–0.962)	0.9863
Chemotherapy		
None	1.000	
Adjuvant only	1.020 (0.728–1.375)	0.4783
Concurrent only	1.019 (0.768–1.316)	0.4679
Both	0.907 (0.528–1.427)	0.6898

Abbreviations: AJCC, American Joint Committee on Cancer; CRI, Bayesian credible interval; HR, hazard ratio; IMRT, intensity-modulated radiation therapy.

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TABLE 4.

Standardized Mortality Ratio Estimates for All-Cause Death of Patients With Oropharyngeal Cancer Who Survived at Least 5 Years After Diagnosis

Subgroup	No. of Patients	Total Person-Years	No. of Observed Deaths	No. of Expected Deaths	SMR (95% CI)	P
Full study population	1699	10,671.05	496	125.67	3.95 (3.60–4.29)	<.0001
HPV status						
Negative	48	176.40	4	2.04	1.96 (0.04–3.88)	.3277
Positive	429	941.34	21	11.45	1.83 (1.05–2.62)	.0372
Period of diagnosis						
1980–1989	133	1531.88	112	20.10	5.57 (4.54–6.60)	<.0001
1990–1999	311	3171.69	186	36.80	5.05 (4.33–5.78)	<.0001
2000–2013	1255	5967.48	198	68.77	2.88 (2.48–3.28)	<.0001
Age at diagnosis, y						
<55	401	3201.20	81	13.01	6.23 (4.87–7.58)	<.0001
55	1298	7469.85	415	112.66	3.68 (3.33–4.04)	<.0001
Sex						
Male	1407	8625.97	377	102.67	3.67 (3.30–4.04)	<.0001
Female	292	2045.08	119	23.00	5.17 (4.24–6.10)	<.0001
Smoking status						
Never	744	4692.57	136	49.37	2.75 (2.29–3.22)	<.0001
Former	571	3514.43	163	49.64	3.28 (2.78–3.79)	<.0001
Current	370	2411.98	194	26.10	7.43 (6.39–8.48)	<.0001
Smoking, pack-y						
>10	680	4220.84	292	54.09	5.40 (4.78–6.02)	<.0001
10	956	5913.59	171	62.47	2.74 (2.33–3.15)	<.0001
Site						
Tonsil	773	4781.10	230	52.39	4.39 (3.82–4.96)	<.0001
Base of tongue	821	5184.03	194	62.65	3.10 (2.66–3.53)	<.0001
Other	105	705.92	72	10.63	6.77 (5.21–8.34)	<.0001
T category						
T1	523	3132.47	98	34.35	2.85 (2.29–3.42)	<.0001
T2	639	4158.36	173	46.77	3.70 (3.15–4.25)	<.0001

Subgroup	No. of Patients	Total Person-Years	No. of Observed Deaths	No. of Expected Deaths	SMR (95% CI)	P
T3	353	2346.27	151	31.02	4.87 (4.09–5.64)	<.0001
T4	183	1006.48	73	13.44	5.43 (4.18–6.68)	<.0001
N category (AJCC 7th ed.)						
N0	218	1621.86	124	25.49	4.86 (4.01–5.72)	<.0001
N1	330	2388.96	101	27.45	3.68 (2.96–4.40)	<.0001
N2	1045	5934.37	228	66.24	3.44 (3.00–3.89)	<.0001
N3	105	698.39	42	6.41	6.56 (4.57–8.54)	<.0001
Neck dissection						
No	1306	7966.37	387	97.50	3.97 (3.57–4.36)	<.0001
Yes	393	2704.67	109	28.17	3.87 (3.14–4.60)	<.0001
IMRT						
No	621	6086.91	369	71.38	5.17 (4.64–5.70)	<.0001
Yes	1078	4584.13	127	54.30	2.34 (1.93–2.75)	<.0001
Radiation dose, Gy						
>70	440	3918.13	222	44.69	4.97 (4.31–5.62)	<.0001
>66–70	622	3057.03	169	38.40	4.40 (3.74–5.07)	<.0001
66	633	3643.70	102	41.89	2.43 (1.96–2.91)	<.0001
Chemotherapy						
No	726	5989.76	301	72.29	4.16 (3.69–4.63)	<.0001
Yes	973	4681.29	195	53.38	3.65 (3.14–4.17)	<.0001

Abbreviations: AJCC, American Joint Committee on Cancer; HPV, human papillomavirus; IMRT, intensity-modulated radiation therapy; SMR, standardized mortality ratio.