The Role of Adjuvant Chemotherapy in Surgically Managed, p16-Positive Oropharyngeal Squamous Cell Carcinoma

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Abstract

IMPORTANCE—Human papillomavirus (HPV)-related oropharyngeal squamous cell carcinoma (OPSCC) has a favorable prognosis, and p16 immunohistochemistry is a surrogate marker of high-risk HPV infection and strong prognosticator. Given this favorable prognosis, treatment de-escalation for p16-positive OPSCC is now being considered with the goal of decreasing treatment-associated morbidity without compromising tumor control. The role of adjuvant chemotherapy in this setting is becoming increasingly unclear.

OBJECTIVE—To compare survival between surgically managed patients with p16-positive OPSCC who received adjuvant chemoradiotherapy and patients who received adjuvant radiotherapy alone.

DESIGN, SETTING, AND PARTICIPANTS—This was a cohort study of patients with OPSCC diagnosed from June 1996 to June 2010, with follow-up through December 2014, at a single tertiary referral center. One hundred ninety-five surgically managed, p16-positive patients without a history of head and neck cancer or distant metastasis at time of diagnosis were included.

EXPOSURES—Patients were dichotomized into adjuvant radiotherapy and adjuvant chemoradiotherapy groups.

MAIN OUTCOMES AND MEASURES—Overall survival was the primary outcome, and disease-free survival was the secondary outcome. Propensity-weighted multivariate Cox proportional hazards analysis was conducted to quantify the effect of adjuvant chemotherapy on survival.

RESULTS—The study included 195 patients with p16-positive, surgically managed OPSCC. Median duration of follow-up was 87 months (interquartile range, 68–116 months). Ninety patients received adjunct chemoradiotherapy (mean age, 54.3 years), 88 patients received adjuvant radiotherapy (mean age, 56.4 years), and 17 patients received surgery alone. The 5-year overall survival rate for patients who received adjuvant chemoradiotherapy was 82% (95% CI, 73%–90%) and 84% (95% CI, 76%–91%) for patients who received adjuvant radiotherapy alone. The 5-year disease-free survival rate for patients who received adjuvant chemoradiotherapy was 79% (95% CI, 71%–88%) and 79% (95% CI, 70%–88%) for patients who received radiotherapy alone. After weighting cases by the inverse probability of receiving adjuvant chemotherapy and controlling for age, comorbidity, smoking, pathological T stage, and pathological N stage, the receipt of adjuvant chemotherapy was not significantly associated with disease-free survival (adjusted hazard ratio, 0.91; 95% CI, 0.59–1.42) but was associated with a statistically insignificant yet clinically meaningful increase in all-cause mortality (adjusted hazard ratio, 1.46; 95% CI, 0.91–2.33).

CONCLUSIONS AND RELEVANCE—Among patients with p16-positive OPSCC managed surgically with adjuvant radiotherapy, the addition of adjuvant chemotherapy provided no additional disease-free survival benefit and was associated with worse overall survival. These results should help inform future clinical trials aiming to deescalate treatment for p16-positive patients.

In the past 30 years, human papillomavirus (HPV) has been identified as a causative agent for a subset of oropharyngeal squamous cell carcinomas (OPSCCs).[1,2] The prevalence of HPV-related OPSCC has risen dramatically over this time, and HPV-positive OPSCC now accounts for the most cases of OPSCC in the United States.[3–6] HPV-positive OPSCC has a characteristic biological, pathological, and clinical profile with distinct risk factors.[1,2,7–9] Importantly, HPV-positive OPSCC has a markedly improved prognosis compared with HPV negative OPSCC.[1,10–13] Given the unique biology of HPV related tumors, p16 immunohistochemistry can be used as a surrogate marker of active, high-risk HPV infection because p16 is markedly overexpressed in tumor cells actively expressing HPVE6.[14,15] p16 status is highly correlated with HPV status and has been shown to be a strong prognostic factor.[13]

Although HPV-positive OPSCC has proven to be a distinct disease entity with a superior prognosis, current OPSCC treatment protocols do not consider HPV status.[16] Traditionally, OPSCC has required aggressive treatment that is associated with high morbidity and poor

functional and quality-of-life outcomes.[17] With the advent of transoral surgical approaches, intensity-modulated radiotherapy, and targeted systemic agents, such as cetuximab, treatment-associated morbidity has decreased but remains substantial. Given the favorable prognosis of HPV-positive OPSCC, many investigators have called for a deintensification of treatment for HPV-positive OPSCC with the goal of further minimizing treatment-associated morbidity without compromising tumor control.[18] Many treatment de-escalation strategies have been proposed, including eliminating chemotherapy for selected patients, replacing platinum based agents with cetuximab, reducing the total radiation dose, and using a single modality approach, but currently there is no consensus on an optimal de-escalation strategy.[19] The role of adjuvant chemotherapy in HPV-positive OPSCC has become particularly unclear, and few studies have adequately investigated the utility of chemotherapy in this setting.

In the present study, we evaluated the effect of adjuvant chemotherapy on survival in a cohort of surgically managed patients with p16-positive OPSCC. Patients who received adjuvant chemoradiotherapy were compared with patients who received adjuvant radiotherapy alone. We hypothesized that the addition of chemotherapy to the treatment regimen would not provide an overall survival (OS) or disease-free survival (DFS) benefit.

Methods

Patient Population

We assembled a cohort of patients with OPSCC diagnosed and treated at Barnes Jewish Hospital in St Louis, Missouri, between June 1996 and June 2010. Inclusion criteria consisted of pathologically confirmed, surgically managed p16- positive OPSCC. p16 Immunohistochemical analysis was conducted retrospectively by a single pathologist (J.S.L.) blinded to patient clinical characteristics and outcome following standard protocols as previously described.[20] Patients with distant metastasis at the time of presentation or with a history of head and neck cancer were excluded. Patients were not compensated and did not provide written informed consent. This study was approved by Washington University School of Medicine's Human Research Protection Office.

Data Acquisition

The Oncology Data Services tumor registry was used to obtain prospectively gathered demographic, clinicopathological, and treatment data. The electronic medical record was used to investigate and resolve any missing values or discrepancies. Vital status was updated through December 2014 using the electronic medical record, and the date of death was confirmed using the Social Security Death Index. Patients with missing values did not differ from patients with complete data in either OS or DFS. Since racial disparities exist in survival of head and neck cancer,[21] we included patient-reported race in our analysis and classified it as white or nonwhite. Smoking history was assessed at the time of diagnosis. Patients who were current smokers or with any history of smoking were considered smokers for our analysis. Comorbid illness at the time of diagnosis was documented using the Adult Comorbidity Evaluation–27[22] and was dichotomized in our analysis as "none to mild" vs "moderate to severe" comorbidity. Pathological tumor, nodal, and overall stage was recorded

from surgical pathology reports in accordance with the *American Joint Committee on Cancer Staging Manual, 7th edition*, criteria.[23] When pathology specimens were unavailable or insufficient, stage was determined using imaging, endoscopy, and physical examination findings.

Treatment

All patients received surgical treatment of the primary site consisting of local tumor excision, partial pharyngectomy, total pharyngectomy, or laryngopharyngectomy. Neck dissection was performed in patients with nodal metastases or those who desired elective dissection. Radiotherapy included conventional external beam radiation therapy or intensity-modulated radiation therapy. Chemotherapeutic regimens consisted of platinum- based agents, taxanes, or cetuximab administered either alone or in combination. Adjuvant radiotherapy or chemoradiotherapy was provided based on the recommendation of a multidisciplinary tumor board that considered the extent of nodal disease, the presence of extracapsular spread, margin positivity, performance status, metabolic criteria, and patient preference. When adjuvant chemoradiotherapy was indicated, it was administered concurrently. For our primary comparison, patients were grouped into adjuvant radiotherapy and adjuvant chemoradiotherapy groups.

Outcomes

Overall survival was the primary outcome measure and was defined as the duration from diagnosis to death from any cause. Disease-free survival was the secondary outcome measure and was defined as the duration from diagnosis to either death from any cause or the first documented recurrence. Recurrences were classified as either locoregional failure or distant metastasis and were considered only in patients who were declared disease-free following initial treatment. Patients who were never disease-free were not classified as having had a recurrence.

Statistical Analysis

Standard descriptive statistics were used to describe the cohort. Differences between treatment groups were explored using χ^2 test or Fisher exact test for categorical data and independent samples *t* test for continuous data. The Kaplan- Meier method with the log-rank test and Cox proportional hazards (PH) analysis were used for univariate survival analysis. To account for differences between treatment groups at baseline, propensity scores were generated using binary logistic regression with the receipt of adjuvant chemotherapy as the dependent variable. Age, sex, race, comorbidity, smoking, pathological T stage, and pathological N stage were used for propensity score estimation. Patients were then weighted according to the inverse probability of receiving adjuvant chemotherapy, and following weighting, covariate balance was assessed between treatment groups. Multivariate, propensity-weighted Cox PH analysis was conducted to evaluate the independent effect of adjuvant chemotherapy on survival. The PH assumption was tested for all variables using log-minus-log plots, and variables significant at the α level of 0.1 in univariate analysis were included in the multivariate model. The effect of adjuvant chemotherapy on survival was presented as an adjusted hazard ratio (aHR) with 95% CI. Following our primary analysis, a sensitivity analysis was performed to determine the effect of a hypothetical unmeasured

binary confounder on the aHR for adjuvant chemotherapy. WinPepi software (version 11.43) was used for sensitivity analysis,[24] and SPSS software (version 22.0; SPSS Inc) was used for all other analyses. All tests of statistical significance were evaluated at the 2-sided α level of .05.

Results

Description of the Cohort

Our cohort consisted of 195 patients with p16-positive, surgically managed OPSCC. The median duration of follow-up among surviving patients was 87 months (interquartile range, 68–116 months). Ninety patients received adjuvant chemoradiotherapy, 88 patients received adjuvant radiotherapy, and 17 patients received surgery alone. The 17 patients who received surgery alone did not differ from patients who received adjuvant therapy in age, sex, race, comorbidity, smoking history, or pathological T stage but did differ in pathological N stage. Patients with stage N2B or greater nodal disease were more than 3 times as likely to receive adjuvant therapy (odds ratio [OR], 3.3; 95% CI, 1.2–9.3]). The 17 patients who received surgery alone were excluded from analyses comparing patients who received adjuvant radiotherapy vs adjuvant chemoradiotherapy. Baseline characteristics of the cohort stratified by adjuvant therapy modality are shown in Table 1. Nodal stage and overall stage were the only variables statistically significantly associated with adjuvant therapy modality; patients with stage N2B or greater nodal disease and patients with overall stage IV disease were significantly more likely to receive adjuvant chemoradiotherapy than radiotherapy alone (OR, 4.92; 95% CI, 2.51–9.66, and OR, 3.42; 95% CI, 1.43–8.17, respectively). Vital status at last follow-up and the number of documented recurrences in each treatment group are shown in Table 2.

Effect of Baseline Characteristics on Survival

The results of univariate and multivariate survival analyses are reported in Table 3. In univariate OS and DFS analyses, age, smoking, pathological T stage, and pathological N stage were significant prognosticators. After controlling for other variables, both age and smoking remained significant independent prognosticators in multivariate OS and DFS analyses. Pathological nodal stage N2C-N3 was not statistically significantly associated with OS in multivariate analysis (aHR, 1.25; 95% CI, 0.75–2.08) but was an independent statistically significant prognostic factor in DFS multivariate analysis (aHR, 2.13;95% CI, 1.34–3.40). Patients with moderate to severe comorbidity had a 1.9- fold increased risk of death from any cause (HR, 1.93; 95% CI, 0.99–3.79) and 1.9-fold increased risk of either death from any cause or recurrence (HR, 1.85; 95% CI, 0.98–3.51) in univariate analyses; however, these relationships vanished after controlling for other variables in multivariate analysis.

Effect of Adjuvant Chemotherapy on Survival

The 5-year OS rate for patients who received adjuvant chemoradiotherapy was 82% (95% CI, 73%–90%)and for patients who received adjuvant radiotherapy alone was 84% (95% CI, 76%–91%). Likewise, the 5-year DFS rate for patients who received adjuvant chemoradiotherapy was 79% (95% CI, 71%–88%) and for patients who received

radiotherapy alone was 79% (95% CI, 70%–88%). After weighting cases by the inverse probability of receiving adjuvant chemotherapy and controlling for age, comorbidity, smoking, pathological T stage, and pathological N stage, the receipt of adjuvant chemotherapy was not associated with DFS (aHR, 0.91; 95% CI, 0.59–1.42) but was associated with a statistically insignificant yet clinically meaningful 46%increased risk of death from any cause (aHR, 1.46; 95% CI, 0.91–2.33). Inverse probability-weighted, adjusted survival curves illustrating the effect of adjuvant chemotherapy on survival are shown in the Figure.

The weighted, aHRs quantifying the relationship between adjuvant chemotherapy and OS and DFS were further adjusted in a sensitivity analysis of a hypothetical unmeasured binary confounder. The results of this sensitivity analysis are shown in Table 4. This analysis demonstrates the extent of confounding by an unmeasured variable that would have to exist to explain our results if adjuvant chemotherapy actually provides a significant survival benefit. For example, for adjuvant chemotherapy to significantly improve OS, an unmeasured binary confounder must have a hazard ratio (HR) for OS greater than 2 and must be substantially more prevalent in the adjuvant chemoradiotherapy group. For adjuvant chemotherapy to significantly improve DFS, an unmeasured binary confounder that has an HR for DFS of 2 must be approximately 50% more prevalent in the adjuvant chemoradiotherapy group.

Discussion

In our investigation of 195 surgically managed patients with p16-positive OPSCC, the addition of chemotherapy to the adjuvant treatment regimen was not found to improve DFS and was associated with worse OS. Because this is an observational study and treatment allocation was not random, confounding by indication[25] may account for the observed lack of benefit of adjuvant chemoradiotherapy over radiotherapy alone. In this study, patients who received adjuvant chemoradiotherapy, compared with patients who received radiotherapy alone, had more severe pathological tumor status, which could account for worse outcome. To account for these differences between treatment groups, we calculated propensity scores and conducted the multivariate analyses after weighting cases by the inverse probability of receiving chemotherapy.

Propensity scores estimate the probability of receiving a treatment given measured baseline covariates and can be used to minimize or eliminate bias due to measured confounders.[26] The goal of using propensity scores is to make the treatment groups as similar as possible and minimize bias with respect to measured covariates to allow for an unbiased comparison of treatment groups. Propensity scores, therefore, allow observational data to more closely approximate randomized clinical trial data. There are several methods for using propensity scores, but inverse probability of treatment weighting (IPTW) is a preferred method for survival analysis.[27] With IPTW, patients who have a high probability of receiving the treatment that they ultimately receive are assigned the lowest weight. Conversely, patients who receive chemotherapy and have a low probability of receiving chemotherapy are weighted more heavily. Through the calculation of propensity scores with IPTW, treatment

groups become balanced with respect to measured covariates, and bias is reduced in the comparison between treatment groups.

While the use of propensity scores minimizes bias due to measured confounders, unmeasured confounding still exists in observational research and can have a substantial effect on study results.[28] Therefore, we conducted a sensitivity analysis to determine the extent of unmeasured confounding that would have to be present to explain our results if adjuvant chemotherapy does provide a significant survival benefit. Our sensitivity analysis indicates that for adjuvant chemotherapy to be significantly beneficial, a hypothetical, unmeasured binary confounder would have to be very strongly associated with survival and greatly disproportionately distributed between our treatment groups. This hypothetical confounder would have to have a greater effect on survival than comorbidity or TNM staging. The presence of such a variable is unlikely. Two variables that are often considered when selecting an adjuvant therapy regimen include extracapsular spread and surgical margin. While these variables have traditionally been prognostic, recent studies indicate that these variables are of limited prognostic value among surgically managed patients with p16-positive OPSCC. Extracapsular spread has poor interobserver and intraobserver reliability[29] and is not associated with OS among surgically managed patients with p16- positive OPSCC.[20,30,31] Likewise, surgical margin is a poor prognosticator among these patients.[32] This is perhaps due to the relative few number of patients who have positive margins and the fact that many patients with positive margins undergo reresection. A limitation to our sensitivity analysis is that we examined the effect a single binary unmeasured confounding variable. It is possible that numerous unmeasured confounding variables exist, each of which biases our observed relationship between adjuvant chemotherapy and survival. Nonetheless, if adjuvant chemotherapy truly provides a survival benefit, the extent of unmeasured confounding required to explain our results would be substantial.

Our results highlight the superior prognosis of patients with p16-positive OPSCC regardless of treatment modality. Both of our treatment groups had 5-year OS rates greater than 80%, and both groups experienced few recurrences. Distant metastasis was the predominant pattern of failure in our cohort, which is consistent with other studies.[18] Because distant failure is more common than local or regional failure in HPV-positive OPSCC, it would be logical to include a systemic chemotherapeutic agent in the treatment regimen. However, our chemoradiotherapy group did not experience fewer recurrences than our radiotherapy group, and DFS was not statistically significantly improved in the chemoradiotherapy group. These findings suggest that the addition of adjuvant chemotherapy in surgically managed, p16-positive OPSCC may be unnecessary.

The use of postoperative adjuvant chemoradiotherapy in locally advanced or high-risk OPSCC is the current standard of care according to the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology.[33] This guideline is based on evidence from 2 large, multicenter randomized clinical trials.[34,35] The NCCN considers the evidence in support of this guideline as category 1–the highest level of evidence. However, the methodology and analyses used in these studies and on which this guideline rests have recently come under critical appraisal.[36] The epidemiology, clinical course, and prognosis of

OPSCC have shifted in recent decades with the advent of HPV-related OPSCC, and the management of these patients must be reconsidered.

To our knowledge, our study is the largest and most thorough investigation of postoperative adjuvant chemotherapy among patients with p16-positive OPSCC. To date, no other studies examining the role of adjuvant chemotherapy in this setting have used propensity scores or included a formal sensitivity analysis. At our institution, Sinha et al[31] investigated the effects of adjuvant chemotherapy on survival among surgically managed patients with p16-positive OPSCC and found no difference in survival between patients treated with adjuvant radiotherapy and those treated with adjuvant chemoradiotherapy. This was a smaller study examining the effects of adjuvant chemotherapy between 24 matched pairs who all exhibited extracapsular spread and who were treated with neck dissection and transoral laser microsurgery. Similarly, Kumar et al[37] found no difference between adjuvant treatment groups among surgically managed, HPV-positive patients with OPSCC. O'Sullivan et al[18] also reported no survival benefit with the addition of adjuvant chemotherapy, with the exception of patients with N2C nodal disease; however, this study investigated adjuvant chemotherapy among nonsurgically managed HPV-positive patients. Our results must be interpreted with caution because observational data have inherent biases. In the absence of randomized studies, our results provide evidence that surgically managed, p16-positive OPSCC may be adequately treated with adjuvant radiotherapy alone.

Limitations

A limitation of our study is the dichotomization of patients into 2 mutually exclusive adjuvant treatment groups. Patients were categorized as having received adjuvant radiotherapy or adjuvant chemoradiotherapy without consideration for total dose or fractionation of radiation received, type or dose of chemotherapeutic agent, or duration of adjuvant therapy. Given the diversity of treatment options, the wide array of patient and physician preferences, and the uniqueness of each patient's disease, it is impossible to fully explore the nuances among different treatment modalities.

Conclusions

Because HPV-related OPSCC is increasingly being recognized as a unique disease entity, new treatment protocols are required to minimize treatment morbidity without sacrificing tumor control. We have shown that for p16-positive patients treated with surgery and adjuvant radiotherapy, the addition of postoperative chemotherapy to the treatment regimen provides no additional DFS benefit and may decrease overall survival. Our findings should inform future clinical trials that seek to optimize the management of p16-positive OPSCC.

Acknowledgments

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Key Points

Question

Is there a survival difference between patients with surgically managed, p16-positive oropharyngeal squamous cell carcinoma who receive adjuvant radiotherapy and patients who receive adjuvant chemoradiotherapy?

Findings

In this cohort study of 195 surgically managed, p16-positive patients, an inverse probability-weighted, multivariate analysis indicated that the receipt of adjuvant chemotherapy is not significantly associated with disease-free survival but is associated with a statistically insignificant yet clinically meaningful increase in all-cause mortality.

Meaning

Among patients with p16-positive oropharyngeal squamous cell carcinoma managed surgically with adjuvant radiotherapy, the addition of adjuvant chemotherapymay be unnecessary.
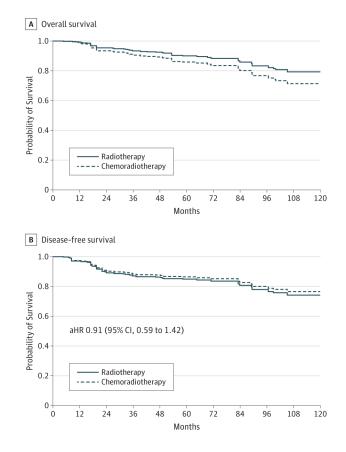
Figure. Inverse Probability-Weighted, Adjusted Survival Curves for Adjuvant Therapy
Survival curves are inverse probability-weighted and adjusted for age, comorbidity, smoking, pathological T stage, and pathological N stage. Adjusted hazard ratio, 1.46; 95% CI, 0.91–2.33. Because this figure is for a predicted model, numbers at risk at not presented.

Table 1

Characteristics of the Cohort Stratified by Adjuvant Therapy Modality

	Adjuvant, No. (%)	
Characteristic	RT (n = 88)	CRT(n = 90)
Age, mean (SD), y	56.4 (9.2)	54.3 (8.0)
Sex		
Male	79 (90)	81 (90)
Female	9 (10)	9 (10)
Race		
White	87 (99)	83 (92)
Nonwhite	1 (1)	7 (8)
Comorbidity		
None	41 (47)	37 (41)
Mild	34 (39)	37 (41)
Moderate	10 (11)	10 (11)
Severe	0 (0)	6 (7)
Unknown	3 (3)	0 (0)
Smoking		
Yes	52 (59)	58 (65)
No	29 (33)	29 (32)
Unknown	7 (8)	3 (3)
Pathological T stage		
T1	33 (38)	32 (36)
T2	37 (42)	35 (39)
T3	8 (9)	14 (15)
T4	8 (9)	9 (10)
Unknown	2 (2)	0 (0)
Pathological N stage		
N0	7 (8)	0 (0)
N1	20 (23)	8 (9)
N2A	20 (23)	9 (10)
N2B	34 (38)	46 (51)
N2C	5 (6)	22 (24)
N3	2 (2)	5 (6)
Pathological overall stage		
I, II	5 (6)	0 (0)
III	17 (19)	8 (9)
IV	66 (75)	82 (91)

Abbreviations: CRT, chemoradiotherapy; RT, radiotherapy.

Table 2

Vital Status and Documented Recurrences Stratified by Adjuvant Therapy Modality

Characteristic	Adjuvant, No. (%)		Difference, % (95% CI)[a]
	RT (n = 88)	CRT (n = 90)	
Vital status			
Alive	64 (73)	70 (78) 5	(−8 to 18)
Dead	24 (27)	20 (22)	
Locoregional failure			
No	86 (98)	89 (99)	1 (−4 to 7)
Yes	2 (2)	1 (1)	
Distant metastasis			
No	83 (94)	82 (91)	3 (−5 to 12)
Yes	5 (6)	8 (9)	

Abbreviations: CRT, chemoradiotherapy; RT, radiotherapy.

[a] Difference between adjuvant treatment groups.

Table 3

Univariate and Inverse Probability-Weighted Multivariate Survival Analysis

	Analysis	
Survival	Univariate, HR (95% CI)	Multivariate, aHR (95% CI)[a]
Overall Survival		
Age: continuous	1.06 (1.03–1.10)	1.06 (1.03–1.09)
Sex: male vs female	2.03 (0.63–6.55)	
Race: white vs nonwhite	1.12 (0.27–4.62)	
Comorbidity: Moderate to severe vs none to mild	1.93 (0.99–3.79)	0.92 (0.52–1.62)
Smoking: yes vs no	4.30 (1.82–10.14)	4.02 (1.94–8.30)
Pathological		
T Stage:T3-T4 vs T1-T2	3.04 (1.70–5.43)	1.38 (0.80–2.37)
N Stage: N2C-N3 vs N0-N2B	2.06 (1.11–3.84)	1.25 (0.75–2.08)
Adjuvant therapy: CRT vs RT	1.05 (0.57–1.93)	1.46 (0.91–2.33)
Disease-Free Survival		
Age: continuous	1.05 (1.02–1.08)	1.04 (1.01–1.06)
Sex: male vs female	1.81 (0.65–4.99)	
Race: white vs nonwhite	1.37 (0.34–5.64)	
Comorbidity: Moderate to severe vs none to mild	1.85 (0.98–3.51)	0.77 (0.44–1.36)
Smoking: yes vs no	3.42 (1.61–7.26)	5.24 (2.55–10.78)
Pathological		
T Stage: T3, T4 vs T1, T2	2.55 (1.47–4.43)	1.31 (0.78–2.20)
N Stage: N2C-N3 vs N0-N2B	1.87 (1.03–3.37)	2.13 (1.34–3.40)
Adjuvant therapy: CRT vs RT	0.93 (0.52–1.66)	0.91 (0.59–1.42)

Abbreviations: aHR, adjusted hazard ratio; CRT, chemoradiotherapy; HR, hazard ratio; RT, radiotherapy.

[a] Inverse probability-weighted multivariate model included all variables significant in univariate analysis at the α level of 0.1 and adjuvant chemotherapy.

Table 4

The Effect of a Hypothetical Unmeasured Binary Confounder on the Adjuvant Chemotherapy Hazard Ratio

UBC Prevalence, %			
CRT Group	RT Group	UBC HR for Overall Survival	Adjuvant Chemotherapy, HR (95% CI) Adjusted for UBC[a]
50	0	4.00	0.58 (0.36–0.93)
90	10	4.00	0.51 (0.32–0.82)
50	0	3.00	0.73 (0.46–1.17)
70	0	3.00	0.61 (0.38–0.97)
90	10	3.00	0.63 (0.39–1.00)
100	0	2.00	0.73 (0.46–1.17)
CRT Group	RT Group	UBC HR for Disease-Free Survival	Adjuvant Chemotherapy, HR (95% CI) Adjusted for UBC[b]
20	0	3.00	0.65 (0.42–1.01)
30	0	3.00	0.57 (0.37–0.89)
30	10	3.00	0.68 (0.44–1.06)
40	10	3.00	0.61 (0.39–0.95)
40	0	2.00	0.65 (0.42–1.01)
50	0	2.00	0.61 (0.39–0.95)
50	10	2.00	0.67 (0.43–1.04)
60	10	2.00	0.63 (0.41–0.98)

Abbreviations: aHR, adjusted hazard ratio; CRT, chemoradiotherapy; HR, hazard ratio; RT, radiotherapy; UBC, unmeasured binary confounder.

[a] Inverse probability-weighted aHR for the relationship between adjuvant chemotherapy and overall survival (aHR, 95% CI, 1.46; 95% CI, 0.91–2.33) after further adjustment for unmeasured binary confounder.

[b] Inverse probability-weighted aHR for the relationship between adjuvant chemotherapy and disease-free survival (aHR, 0.91; 95% CI, 0.59–1.42) after further adjustment for unmeasured binary confounder.