


## ORIGINAL ARTICLE

# Serum lactate dehydrogenase is a predictive biomarker in patients with oropharyngeal cancer undergoing radiotherapy: Retrospective study on predictive factors

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## Abstract

**Background:** The present study aimed to evaluate the prognostic factors in human papillomavirus (HPV)-positive and HPV-negative oropharyngeal cancer (OPC) treated with definitive radiotherapy.

**Methods:** We retrospectively evaluated 101 patients with OPC who underwent definitive radiotherapy between 2008 and 2018.

**Results:** The median follow-up period of the surviving patients was 68 months (range, 8–164 months). The 5-year overall survival rate was 69.8%. Univariate analyses revealed that poor survival was associated with male sex, smoking  $\geq 30$  pack-years, Eastern Cooperative Oncology Group performance status  $\geq 1$ , tumor-node-metastasis (TNM) stage III-IV (8th edition), HPV-negativity, serum lactate dehydrogenase (LDH)  $\geq 202$ , C-reactive protein/albumin ratio  $\geq 0.15$ , and lymphocyte-to-monocyte ratio  $< 2.90$ . In multivariate analyses, poor survival was independently correlated with smoking  $\geq 30$  pack-years ( $p < 0.01$ ) and LDH  $\geq 202$  ( $p = 0.02$ ).

**Conclusions:** The present study suggested that high LDH levels predicted poor survival after definitive radiotherapy for patients with both HPV-positive and HPV-negative OPC.

## KEYWORDS

head and neck squamous cell carcinoma, human papillomavirus, oropharyngeal cancer, radiotherapy, serum lactate dehydrogenase

## 1 | INTRODUCTION

Over the last two decades, there has been a significant increase in the incidence of oropharyngeal cancer (OPC)

due to human papillomavirus (HPV) infection in the United States and Europe.<sup>1,2</sup> Among high-risk variants, HPV16 accounts for almost 85% of OPC cases in Western countries.<sup>1</sup> Multiple studies have established that patients

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with HPV-positive OPC have a better prognosis than patients with HPV-negative.<sup>3,4</sup> Therefore, HPV-positive OPC shows distinct epidemiological, clinical, and molecular features when compared to HPV-negative OPC, and tumor HPV status is recognized as the strongest independent prognostic factor for radiotherapy (RT) outcomes.<sup>1,4–8</sup> Although the clinical and molecular-genetic characteristics of HPV-positive and HPV-negative OPC clearly differ, whether the prognostic factors for these cancers are also distinct remains unclear.<sup>9</sup>

Currently, the eighth edition of the International Union Against Cancer (UICC)/American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) classification system for OPC considers the

HPV status.<sup>10</sup> The system accurately reflected the superior survival outcomes of HPV-positive OPC. Additionally, it is well known that tobacco smoking history is a strong prognostic factor for survival in patients with OPC.<sup>11</sup> Similarly, serum lactate dehydrogenase (LDH),<sup>12–14</sup> neutrophil-to-lymphocyte ratio (NLR),<sup>15,16</sup> lymphocyte-to-monocyte ratio (LMR),<sup>17,18</sup> and C-reactive protein (CRP)/albumin ratio (CRP/Alb)<sup>19</sup> have been identified as prognostic factors in several types of cancers, including nasopharyngeal cancer (NPC), lung cancer, and hepatocellular carcinoma. These markers are more readily available and more cost-effective to assess than others. Nevertheless, the prognostic significance of these hematological markers in OPCs has

**TABLE 1** Clinicopathological characteristics of patients with oropharyngeal cancer (no. of patients = 101) according to HPV status

	HPV-positive (N = 50)	HPV-negative (N = 51)	p-value
Median age at diagnosis (range)	63 (43–85)	65 (38–85)	0.34
Sex			0.46
Female	13 (26.0%)	10 (19.6%)	
Male	37 (74.0%)	41 (80.4%)	
Smoking (pack-years) [median (range)]	20 (0–105)	40 (0–150)	<0.01
ECOG-PS			<0.01
0	43 (86.0%)	33 (64.7%)	
≥1	7 (14.0%)	18 (35.3%)	
Treatment			0.32
CRT	26 (52.0%)	27 (52.9%)	
BRT	11 (22.0%)	6 (11.8%)	
RT alone	13 (26.0%)	18 (35.3%)	
T classification			0.17
1–2	36 (72.0%)	30 (58.8%)	
3–4	14 (28.0%)	21 (41.2%)	
N classification			0.09
1–2	40 (80.0%)	18 (35.3%)	
3–4	10 (20.0%)	33 (64.7%)	
TNM stage (7th edition)			0.17
I	2 (4.0%)	4 (7.8%)	
II	3 (6.0%)	7 (13.7%)	
III	6 (12.0%)	18 (35.3%)	
IV	39 (78.0%)	22 (43.2%)	
TNM stage (8th edition)			<0.01
I	32 (64.0%)	4 (7.8%)	
II	6 (12.0%)	7 (13.7%)	
III	12 (24.0%)	17 (33.3%)	
IV	0 (0%)	23 (45.2%)	

Abbreviations: BRT, bioradiotherapy; CRT, chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; HPV, human papillomavirus; PS, performance status; RT, radiotherapy; TNM, tumor-node-metastasis.

not been fully elucidated. Therefore, in this study, the medical records of patients with OPC treated with definitive RT were retrospectively analyzed to identify distinct prognostic subsets of OPC.

## 2 | MATERIALS AND METHODS

### 2.1 | Patients

This retrospective study was conducted in full accordance with the World Medical Association Declaration of Helsinki and approved by our institutional review board (R02-112), and all patients provided informed consent for definitive RT. Between August 2008 and December 2018, we identified 150 consecutive patients with OPC who underwent RT alone or chemoradiotherapy (CRT) at our institution. We excluded patients who had follow-up durations of less than 6 months without any specific events. In addition, two patients with distant metastasis at the time of diagnosis were excluded. Immunohistochemistry (IHC) for HPV/p16 expression was performed as previously described.<sup>8</sup> In this study, 44 patients with unknown HPV status were excluded. Blood test data within 4 weeks before the first day of RT treatment were available for all but three patients who were excluded from the analyses. Therefore, 101 patients were eligible for the analysis. The characteristics of the study patients are summarized in Table 1. Pretreatment evaluations included a complete history, physical examination, routine blood tests, and laryngoscopy. All patients were examined by gastrointestinal fibroscopy and whole-body computed tomography (CT), with or without head and neck magnetic resonance imaging (MRI). Staging was performed according to the UICC TNM classification system (7th and 8th editions).<sup>10</sup> Based on the recommendations from the multidisciplinary tumor board, patients were treated with either RT alone or CRT. Forty-nine patients (48.5%) underwent ipsilateral or bilateral neck dissection before definitive RT. Additionally, volume reduction surgery of the primary tumor was performed in 24 patients (23.8%) before RT.

### 2.2 | Treatment

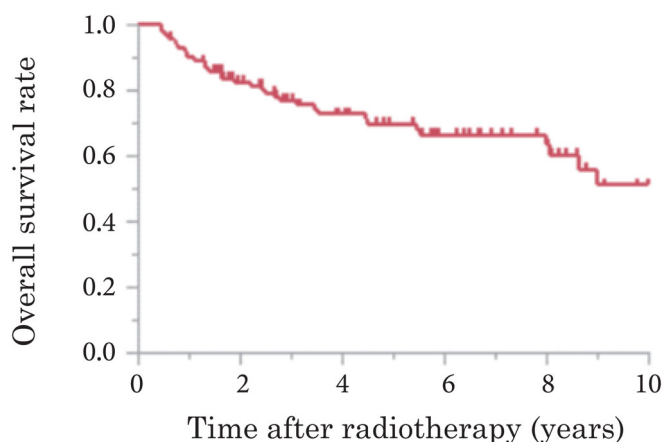
All 101 patients were treated using a two-step intensity-modulated RT (IMRT) technique. At our institution, a two-step method is used for head and neck cancers instead of the simultaneous integrated boost method.<sup>20</sup> The procedure of two-step IMRT has been previously described in detail.<sup>8</sup> In short, whole neck RT of 44.0–50.0 Gy/22–25 fractions was delivered, followed by boost doses to the high-risk clinical target volume (CTV) up to a total dose of

70.0 Gy/35 fractions. The daily prescribed dose to the planning target volume (PTV) was 2 Gy in all patients. The prescribed dose was normalized to 95% of the PTV.

Between 2008 and 2018, 31 patients (30.7%) with TNM stage I or II disease, major comorbidity, or poor performance status were treated with RT alone. Concurrent chemotherapy was administered to 70 patients (69.3%). Between 2005 and 2018, 49 patients (48.5%) were treated with RT and three cycles of concomitant cisplatin (80.0–100 mg/m<sup>2</sup> every 3 weeks). Four patients (4.0%) with poor renal function were treated with weekly carboplatin (five areas under the curve). Between 2013 and 2018, 17 elderly patients (16.8%) with poor renal function were treated with weekly cetuximab (250.0 mg/m<sup>2</sup>).

### 2.3 | Statistical analyses

Comparisons between the HPV-positive and HPV-negative OPC groups were performed using *t* tests for continuous variables and Fisher's exact tests for categorical variables. Time-to-event analyses were performed from the start of definitive RT to the occurrence of the event. Receiver-operating characteristic (ROC) curve analysis was used to determine the most appropriate cut-off points for hematological biomarkers, including LDH, NLR, LMR, and CRP/Alb. The Kaplan–Meier method and log-rank test were used to compare the overall survival (OS) curves. OS was defined as the time to death from any cause. In addition, potential prognostic factors were evaluated using Cox proportional hazards models, and the results were reported as hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). Significant



**FIGURE 1** Overall survival (OS) after definitive radiotherapy in patients with human papillomavirus-positive and -negative oropharyngeal cancer. The 5-year OS was 69.8% (95% confidence interval: 0.59–0.79) [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

**TABLE 2** Univariate and multivariate analysis results of patients with oropharyngeal cancer

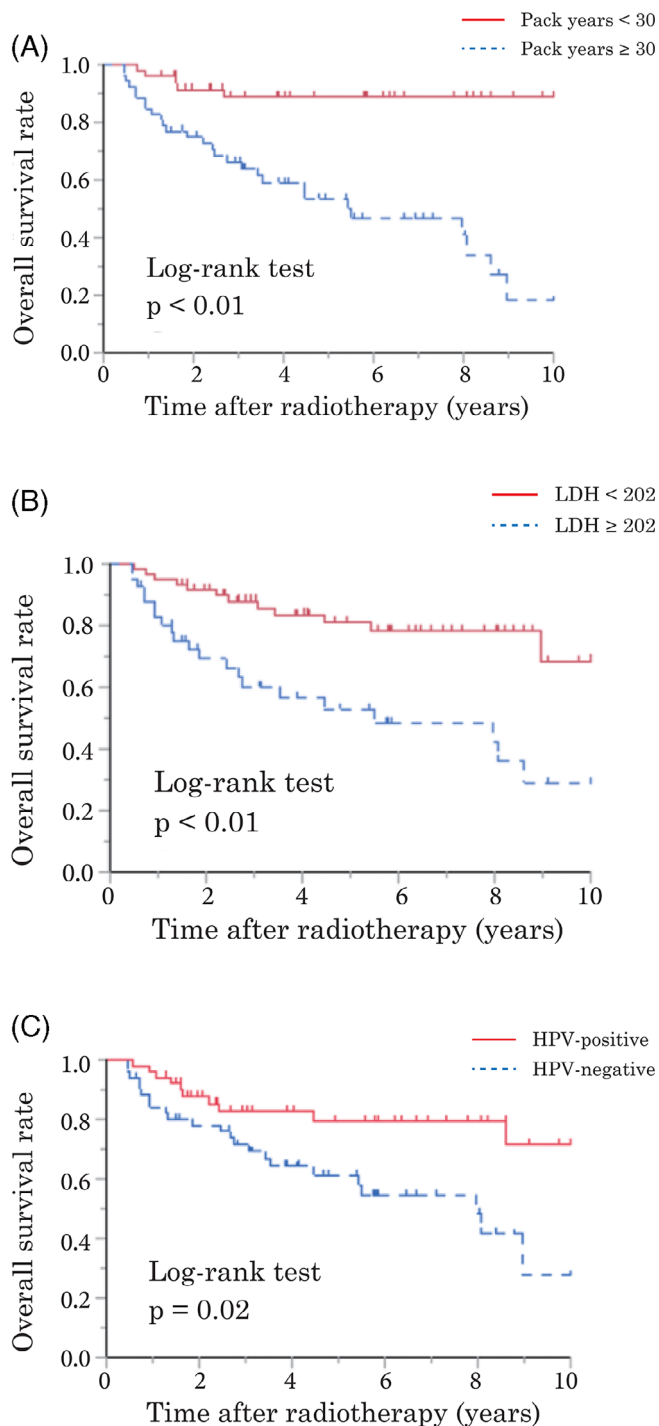
Parameter	Patients (N = 101)	5-year survival (%)	Univariate analysis		Multivariate analysis	
			HR (95% CI)	p-value	HR (95% CI)	p-value
Age (years)						
<65	51	75.3	1	0.23		
≥65	50	64.6	1.52 (0.77–3.11)			
Sex						
Female	23	89.8	1	<0.01	1	0.48
Male	78	63.7	4.36 (1.53–18.4)		1.61 (0.45–7.78)	
Smoking (pack-years)						
<30	49	88.8	1	<0.01	1	<0.01
≥30	52	53.5	5.78 (2.55–15.5)		4.20 (1.54–13.6)	
ECOG-PS						
0	76	77.1	1	0.01	1	0.28
≥1	25	47.3	2.59 (1.25–5.20)		1.53 (0.70–3.27)	
Treatment						
CRT or BRT	70	62.8	1	0.22		
RT alone	31	82.9	0.62 (0.28–1.31)			
TNM stage (7th edition)						
I-III	40	74.9	1	0.32		
IV	61	66.9	1.44 (0.71–3.07)			
TNM stage (8th edition)						
I-II	49	80.8	1	<0.01		
III	52	59.7	2.74 (1.35–6.03)			
HPV						
Positive	50	79.4	1	0.02	1	0.58
Negative	51	61.3	2.37 (1.17–5.09)		1.25 (0.58–2.81)	
LDH						
<202	60	80.9	1	<0.01	1	0.02
≥202	41	52.9	3.48 (1.75–7.27)		2.38 (1.13–5.27)	
CRP/Alb						
<0.15	35	75.6	1	<0.01	1	0.67
≥0.15	66	59.6	2.57 (1.30–5.22)		1.20 (0.52–2.78)	
NLR						
<6.10	82	72.7	1	0.16		
≥6.10	19	56.5	1.77 (0.79–3.66)			
LMR						
<2.90	40	54.9	1	<0.01	1	0.13
≥2.90	61	87.6	0.32 (0.15–0.63)		0.51 (0.21–1.21)	

Abbreviations: Alb, albumin; BRT, bioradiotherapy; CI, confidence interval; CRP, C-reactive protein; CRT, chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; HPV, human papillomavirus; HR, hazard ratio; LDH, serum lactate dehydrogenase; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PS, performance status; RT, radiotherapy; TNM, tumor-node-metastasis.

factors identified in the univariate analyses were included in the multivariate model by backward elimination of the insignificant explanatory variables. All analyses were performed using JMP software (version 14.0.0; SAS Institute, Cary, NC), and differences were considered statistically significant at  $p < 0.05$ .

### 3 | RESULTS

The median follow-up period of the surviving patients was 68 months (range, 8–164 months). Figure 1 shows the OS after RT for patients with HPV-positive and HPV-negative OPC. The 5-year OS was 69.8% (95% CI: 0.59–



**FIGURE 2** Kaplan–Meier's analysis of overall survival (OS) rates in patients with human papillomavirus (HPV)-positive and -negative oropharyngeal cancer. OS according to smoking (A), serum lactate dehydrogenase (LDH) (B), and HPV status (C) [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

0.79). The cut-off values obtained by ROC for LDH, CRP/Alb, NLR, and LMR were 202, 0.15, 6.10, and 2.90, respectively.

The results of the univariate and multivariate analyses of prognostic factors are shown in Table 2.

Univariate analyses revealed that poor survival was associated with male sex, smoking  $\geq 30$  pack-years, Eastern Cooperative Oncology Group performance status (ECOG-PS)  $\geq 1$ , TNM stage III-IV (8th edition), HPV-negativity, LDH  $\geq 202$ , CRP/Alb  $\geq 0.15$ , and LMR  $< 2.90$ . In multivariate analyses, poor survival was independently correlated with smoking  $\geq 30$  pack-years and LDH  $\geq 202$  (Figure 2) but not HPV status. To eliminate confounding bias between HPV status and TNM stage (8th edition), the TNM stage was excluded from the multivariate analysis, despite showing a significant result in the univariate analysis.

Patients were divided into HPV-positive and HPV-negative OPC groups and potential prognostic factors were subsequently assessed in univariate analyses. The results for the HPV-positive and HPV-negative OPC groups are shown in Tables 3 and 4, respectively. In patients with HPV-positive OPC, poor survival was associated with smoking  $\geq 30$  pack-years, LDH  $\geq 202$ , and LMR  $< 2.90$ . In patients with HPV-negative OPC, univariate analyses identified male sex, smoking  $\geq 30$  pack-years, TNM stage IV (7th edition), LDH  $\geq 202$ , and CRP/Alb  $\geq 0.15$  as significant predictors of poor survival (Figure 3).

## 4 | DISCUSSION

In this study, the prognostic factors for patients with OPC were evaluated. Our study suggested that poor survival might be independently associated with high LDH levels in patients with OPC, regardless of HPV status. It is noteworthy that high LDH levels may be a stronger poor prognostic factor than HPV status and TNM stage (both 7th and 8th editions) in this study. Moreover, as is well-known from previous studies, tobacco smoking affects treatment response and negatively affects patients with OPC.<sup>4,11,21</sup>

Elevated LDH levels have been identified as a negative prognostic indicator for many solid tumors, including non-Hodgkin's lymphoma,<sup>12</sup> germ cell tumors,<sup>13</sup> and small-cell lung cancer.<sup>14</sup> The prognostic significance of serum LDH levels in NPC has been investigated in several retrospective studies.<sup>22–24</sup> High levels of serum LDH were found to be correlated with a larger tumor burden in NPC.<sup>25</sup> In addition, a high LDH level was associated with the extent of locoregional control and/or distant metastasis events and could predict a poor prognosis.<sup>25</sup> However, there are limited data regarding the use of pre-treatment serum LDH to predict the prognosis of patients with OPC. In both HPV-positive and HPV-negative OPC, OS was considerably worse in patients with higher LDH levels than in those with lower levels. To the best of our knowledge, this is the first study to indicate that LDH

**TABLE 3** Univariate analysis results of patients with HPV-positive oropharyngeal cancer

Parameter	Patients (N = 50)	5-year survival (%)	HR (95% CI)	p-value
Age (years)				
<65	27	87.4	1	0.14
≥65	23	70.9	12.7 (0.74–12.3)	
Sex				
Female	13	92.3	1	0.17
Male	37	74.3	3.47 (0.65–64.1)	
Smoking (pack-years)				
<30	30	89.5	1	0.03
≥30	20	63.8	4.21 (1.15–19.7)	
ECOG-PS				
0	43	83.5	1	0.13
≥1	7	53.6	3.13 (0.67–11.3)	
Treatment				
CRT or BRT	37	75.6	1	0.85
RT alone	13	84.6	0.87 (0.18–3.25)	
TNM stage (7th edition)				
I-III	11	80.8	1	0.90
IV	39	78.8	1.11 (0.27–7.37)	
TNM stage (8th edition)				
I-II	38	81.4	1	0.22
III	12	74.1	2.31 (0.58–8.23)	
LDH				
<202	34	85.7	1	0.04
≥202	16	66.2	3.59 (1.01–14.2)	
CRP/Alb				
<0.15	34	84.1	1	0.29
≥0.15	16	70.7	1.98 (0.55–7.15)	
NLR				
<6.10	42	79.7	1	0.33
≥6.10	8	75.0	2.07 (0.43–7.68)	
LMR				
<2.90	17	60.5	1	<0.01
≥2.90	33	88.6	0.18 (0.04–0.66)	

Abbreviations: Alb, albumin; BRT, bioradiotherapy; CI, confidence interval; CRP, C-reactive protein; CRT, chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; HPV, human papillomavirus; HR, hazard ratio; LDH, serum lactate dehydrogenase; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PS, performance status; RT, radiotherapy; TNM, tumor-node-metastasis.

levels are associated with poor prognosis and that they can be an independent prognostic marker for patients with OPC regardless of HPV status. In addition, the results would imply that potentially LDH could be a biomarker for nonoropharyngeal head and neck cancers.

Although the prognostic value of LDH has been studied extensively, the underlying mechanism linking LDH

to poor survival remains unknown. It has been hypothesized that serum LDH levels may reflect the extent of hypoxia in tumor cells, since it catalyzes the transformation of pyruvate to lactate under hypoxic conditions.<sup>26,27</sup> Due to rapid cancer cell proliferation, high metabolic demands, and functional angiogenesis, hypoxia is a characteristic feature of locally advanced solid tumors.<sup>28</sup> In

Parameter	Patients (N = 51)	5-year survival (%)	HR (95% CI)	p-value
Age (years)				
<65	24	63.9	1	0.62
≥65	27	58.9	1.24 (0.53–2.96)	
Sex				
Female	10	87.5	1	<0.01
Male	41	55.2	7.51 (1.57–134)	
Smoking (pack-years)				
<30	19	88.2	1	<0.01
≥30	32	47.9	7.02 (2.05–43.9)	
ECOG-PS				
0	33	69.7	1	0.13
≥1	18	44.3	1.81 (0.76–4.19)	
Treatment				
CRT or BRT	33	50.1	1	0.06
RT alone	18	81.4	0.41 (0.14–1.04)	
TNM stage (7th edition)				
I–III	29	72.2	1	0.03
IV	22	48.2	2.51 (1.09–6.06)	
TNM stage (8th edition)				
I–II	11	79.6	1	0.13
III	40	56.7	2.34 (0.80–9.98)	
LDH				
<202	26	75.7	1	<0.01
≥202	25	45.5	3.14 (1.32–8.26)	
CRP/Alb				
<0.15	31	69.9	1	0.01
≥0.15	20	47.9	2.98 (1.28–7.47)	
NLR				
<6.10	40	66.1	1	0.37
≥6.10	11	42.4	1.56 (0.57–3.80)	
LMR				
<2.90	23	50.6	1	0.11
≥2.90	28	68.7	0.51 (0.22–1.16)	

**TABLE 4** Univariate analysis results of patients with HPV-negative oropharyngeal cancer

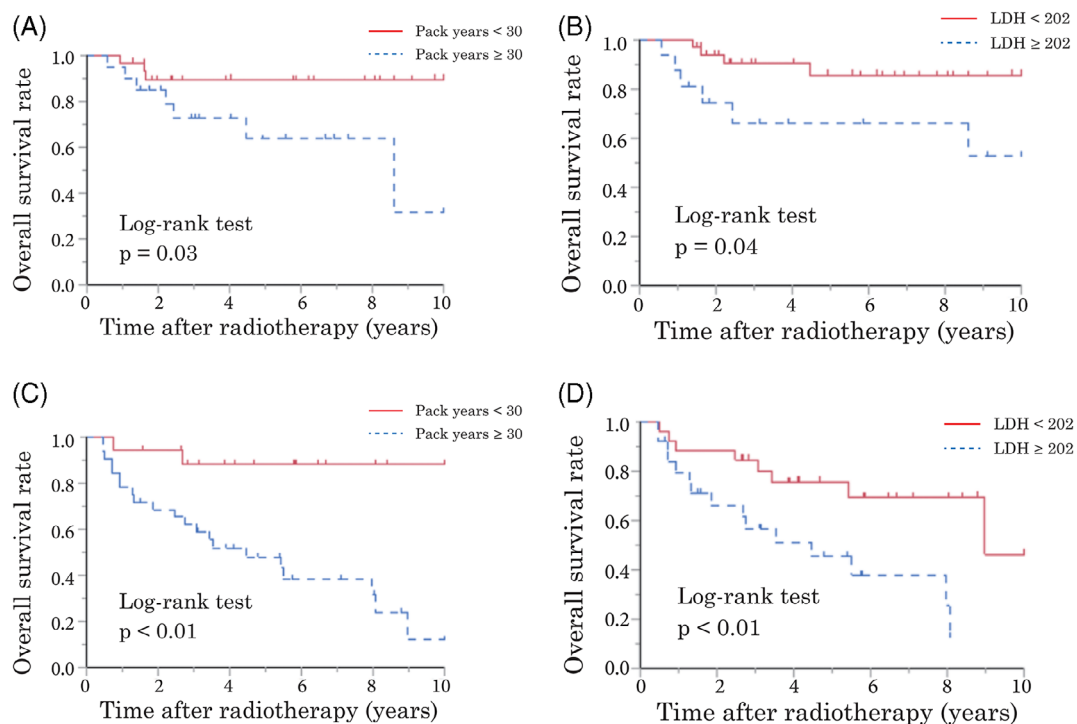
Abbreviations: Alb, albumin; BRT, bioradiotherapy; CI, confidence interval; CRP, C-reactive protein; CRT, chemoradiotherapy; ECOG, Eastern Cooperative Oncology Group; HPV, human papillomavirus; HR, hazard ratio; LDH, serum lactate dehydrogenase; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PS, performance status; RT, radiotherapy; TNM, tumor-node-metastasis.

addition, it is well known that hypoxic tumor cells are radioresistant and/or chemoresistant.<sup>29</sup> These findings indicate that high LDH levels related to tumor hypoxia might lead to poor survival after RT.

Based on their better outcomes, several ongoing clinical studies are evaluating the applicability of de-escalating treatment for patients with HPV-positive OPC.<sup>30–34</sup> Recently, two clinical trials failed to show noninferior

tumor control and reduced toxicity.<sup>33,34</sup> Mehanna et al. performed an open-label randomized controlled phase 3 trial, De-ESCALaTE HPV, to investigate the effect of substituting cisplatin with cetuximab on RT in patients with advanced HPV-positive OPC with no or little tobacco smoking history.<sup>33</sup> The results showed no difference in overall severe toxicity between the two groups. Surprisingly, they demonstrated that the cetuximab group showed





**FIGURE 3** Kaplan–Meier analysis of overall survival (OS) rates. OS according to smoking (A) and serum lactate dehydrogenase (LDH) (B) in patients with human papillomavirus (HPV)-positive oropharyngeal cancer (OPC). OS according to smoking (C) and LDH (D) in patients with HPV-negative OPC [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

significantly worse 2-year OS and disease recurrence rates compared with the cisplatin group. In their study, LDH levels were not used as stratification factors. On the other hand, de-escalation of dose and target volume in RT has been tested in phase 2 clinical trials, yet the results are currently immature.<sup>35,36</sup> Foster et al.<sup>35</sup> and Seiwert et al.<sup>36</sup> also stratified patients for de-escalated treatment according to smoking history but not LDH levels. Although tobacco smoking history, a strong prognostic factor, was often used in the stratification for de-escalated treatment as mentioned above, the results of these trials were not successful. Therefore, based on the present data, LDH might be useful for risk stratification when considering de-escalated strategies for HPV-positive OPC.

Additionally, in this study, high LDH levels were a stronger poor prognostic factor than HPV status and TNM stage (both 7th and 8th editions). However, the relatively small sample size and heterogeneous patient demographics of the present study might be associated with the insignificant differences in survival according to HPV status and TNM stage. With regards to TNM stage specifically, the univariate analysis demonstrated a significant difference in OS according to the 8th edition TNM stage but not the 7th edition. Whereas the 7th edition staging system considered only the anatomical extent of disease,<sup>10</sup> the 8th edition considered HPV status. Our present data suggest that the 8th edition is

suitable for staging patients with OPC, as stated in a previous study.<sup>37</sup>

The present study has several limitations, including its retrospective design, relatively small sample size, and heterogeneous patient characteristics. However, our multivariate analysis incorporating patients' background factors and treatment modalities addressed this heterogeneity to a certain extent. In addition, LDH was confirmed as a reproducible prognostic marker in patients with both HPV-positive and HPV-negative OPC. Moreover, we also assessed prognostic factors with respect to HPV status; however, the insufficient sample size of the subgroups precluded multivariate analyses. Furthermore, the heterogeneous patient characteristics might have been due to the time background between 2008 and 2018. However, the standard RT treatment for OPC did not change during this period.<sup>36,37</sup> In addition, we excluded patients with unknown HPV status from this study in order to increase the cohort's homogeneity. Further, the follow-up period was sufficiently long (68 months) to assess survival outcomes. Therefore, we believe that the present study provides valuable data that can be reliably adopted in daily clinical practice and act as the foundation for future clinical trials.

In conclusion, the present study suggested that high LDH levels might be a predictive factor for poor survival after definitive RT for patients with HPV-positive and HPV-



negative OPC. High LDH levels may be a stronger prognostic factor than HPV status and TNM stage. As this is a small sample size with wide confidence intervals and retrospective, the findings are really hypothesis that require validation in a larger well designed prospective trial.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

## AUTHOR CONTRIBUTIONS

Takuya Uehara, Hiroshi Doi, Masahiro Inada, Saori Tatsuno, Yutaro Wada, Yasuo Oguma, Kazuki Ishikawa, Kiyoshi Nakamatsu, Makoto Hosono, and Yasumasa Nishimura performed radiotherapy. Takuya Uehara, Hiroshi Doi, and Masahiro Inada conceived this study, analyzed the data, and drafted the manuscript. Yasumasa Nishimura supervised the project. All authors read and approved the final manuscript.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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