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Matched-pair analysis of survival in patients with poorly differentiated versus well and moderately differentiated hypopharyngeal squamous cell carcinoma

Xin Xia, MD[a], Ya Liang, MD[b], Yingying Zhu, MD, PhD[a], Xiaoli Zhu, MD[a], Wenwen Diao, MD, PhD[a], Xingming Chen, MD, PhD[a,*]

Abstract

Hypopharyngeal squamous cell carcinoma (HPSCC) is among the most common malignances of the head and neck and is associated with a poor prognosis. Although both differentiation and tumor-node-metastasis stage affect tumor aggressiveness, the effect of differentiation on the prognosis of HPSCC at different stages is unclear. The aim of this study was to compare survival outcomes between patients with poorly differentiated versus well-differentiated and moderately differentiated HPSCC.

Patients with well/moderately differentiated and poorly differentiated HPSCC were matched based on age, sex, smoking status, alcohol use, comorbidity score, tumor stage, and therapeutic strategies. The Kaplan-Meier curve and Cox proportional hazards model were used to analyze survival. A total of 204 patients with newly diagnosed HPSCC were included after matching 102 well/moderately differentiated cases and 102 poorly differentiated cases from Peking Union Medical College Hospital.

Patients with well/moderately differentiated HPSCC had significantly better disease-specific survival (P = .003) and overall survival (P = .006) than patients with poorly differentiated HPSCC. Additionally, multivariable analysis indicated that increased differentiation was associated with a significantly reduced risk of overall death (adjusted hazard ratio, 0.51; 95% confidence interval, 0.34–0.78, P = .002), and death due to disease (adjusted hazard ratio, 0.44; 95% confidence interval, 0.28–0.69, P < .001).

Survival outcomes differed significantly between the well/moderately differentiated and poorly differentiated HPSCC patients. Treatment strategies based on the level of pathological differentiation might be necessary to improve survival outcomes in patients with HPSCC.

Abbreviations: CI = confidence interval, DSS = disease-specific survival, HPSCC = hypopharyngeal squamous cell carcinoma, HR = hazard risk, OS = overall survival.

Keywords: differentiation, hypopharyngeal neoplasms, matched-pair analysis, squamous cell carcinoma, survival analysis

1. Introduction

Hypopharyngeal squamous cell carcinoma (HPSCC), arising from the mucosa of the upper aerodigestive tract, is generally associated with a poor prognosis, with a 5-year survival rate of approximately 30% to 35%.[1] Advanced stages are more frequent in patients with HPSCC compared with head and neck cancers outside the hypopharynx, which is a challenge for treatment.[2] Treatment of HPSCC is generally determined according to the National Comprehensive Cancer Network guidelines and expert consensus on surgery and comprehensive treatment of hypopharyngeal carcinoma of different countries and regions.[3,4] The overall stage and adverse features (extranodal extension, positive margins, close margins, pT3 or pT4 primary, pN2 or pN3 nodal disease, perineural invasion, vascular invasion, lymphatic invasion) are always used as prognostic markers to guide treatment decisions for HPSCC patients.[5] However, the prognosis differs between patients with well/moderately differentiated and poorly differentiated HPSCC.[6]

Although both differentiation and tumor-node-metastasis (TNM) stage are known to affect tumor aggressiveness, the effect of differentiation on the prognosis of HPSCC at different stages is unclear. Furthermore, the survival outcome of HPSCC is known to be closely associated with a variety of other clinical

XX and YL contributed equally to this study.

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All data generated or analyzed during this study are included in this published article.

[a] Department of Otolaryngology-Head and Neck Surgery, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, China, [b] Department of Otorhinolaryngology, Affiliated Hospital of Guizhou Medical University, Guizhou, China.

** Correspondence: Xingming Chen, Department of Otolaryngology-Head and Neck Surgery, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences, No. 1, Shuaifuyuan, Wangfujing, Beijing 100730, China (e-mail: xingming.chen@hotmail.com).*

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features, lifestyle factors, fundamental role of mitochondria on survival and response to treatment, and epidemiologic variables, and these prognostic factors may further confound survival analysis.[7–12] Matched-pair analysis allows for the removal of such confounding factors and a more accurate comparison of survival.

Therefore, in this study, we performed a matched-pair case-control analysis of patients with well/moderately differentiated and poorly differentiated HPSCC and compared survival to determine whether differentiation has any effect on survival. To the best of our knowledge, this is the first matched-pair design controlling variables of known prognostic significance for survival analysis of HPSCC with different differentiation stages.

2. Methods

2.1. Study participant

A total of 1046 patients with newly diagnosed, pathologically confirmed, and untreated HPSCC were reviewed at the Peking Union Medical College Hospital between January 2003 and December 2017. The study protocol was approved by the Ethics Committee of the Peking Union Medical College Hospital. The requirement for written informed consent was waived because of the retrospective nature of the study.

Epidemiologic and clinical information including age, sex, comorbidity score, tobacco and alcohol consumption, tumor site, TNM stage, treatment strategies, and pathological findings were obtained from the participants for this matched-pair analysis. Comorbidity scores were classified according to the Adult Comorbidity Evaluation-27.[13] "Smokers" were defined as those who had smoked more than 100 cigarettes in their lifetime, whereas "non-smokers" had smoked 100 cigarettes or fewer. "Drinkers" were defined as those who drank alcoholic beverages at least once a week for 1 year or longer; otherwise, they were defined as "non-drinkers."[14] TNM stages were identified in all participants according to the TNM classification criteria designated by the American Joint Committee on Cancer.

For the purpose of matched-pair case-control analysis, only cases of pathologically confirmed poorly differentiated or well/moderately differentiated primary HPSCC were enrolled in the study in order to compare survival outcomes of these grades of differentiation. The exclusion criteria were as follows: (1) patients with no clear medical documentation or were lost during follow-up; (2) non-squamous cell carcinoma; (3) secondary onset; (3) recurrent disease; (4) no initial treatment or only palliative care; (5) chronic diseases affecting the patients' survival; and (6) cases with other tumors or tumor-related diseases.

2.2. Matching criteria

The matching variables in the current study included age, sex, smoking status, alcohol use, primary tumor site, comorbidity score, disease stage, and therapeutic strategies. The matched-pair data were followed at a 1:1 ratio for the well/moderately differentiated and poorly differentiated HPSCC cases. All pathological diagnoses were confirmed by 2 pathologists. The pairing criteria were as follows: (1) age difference within 5 years; (2) same sex (male or female); (3) same smoking status (non-smoker or smoker); (4) same alcohol use (non-drinker or drinker); (5) same primary tumor site (pyriform sinus, postcricoid region or posterior wall of the hypopharynx); (6) comorbidity score (none to mild or moderate to severe); (7) same TNM stage; and (8) same therapeutic strategies (primary surgery and primary (chemo)radiation).

2.3. Patient's follow-up

Patients were followed up from the date of treatment with regularly scheduled clinical and radiographic examinations. The primary endpoint was overall survival (OS), defined as the time from the date of starting treatment to the date of death from any cause or the last follow-up date. The secondary endpoint was disease-specific survival (DSS), defined as the time from the date of starting treatment to the date of death from disease or last follow-up. Patients were considered alive and free of disease recurrence if disease absence was documented on the date of the last follow-up in December 2020. All patients were followed up for a minimum of 3 years or until death.

2.4. Statistical analyses

Data were analyzed using SPSS (SPSS for Windows version 22.0; IBM Corporation, Armonk, NY). The statistical test used for matched-pair analysis was case-control matching. Differences between the well/moderately differentiated and poorly differentiated HPSCC groups in DSS and OS were compared using the Kaplan-Meier method and the log-rank test for equality of survival curves. Multivariate analysis was performed using the Cox proportional hazards model. All statistical tests were 2-tailed, and P values <.05 were considered statistically significant.

3. Results

3.1. Demographic and clinical characteristics

Based on the inclusion and exclusion criteria, a total of 102 pairs of patients with HPSCC were included in this matched-pair analysis. Patient characteristics of the well/moderately differentiated and poorly differentiated groups are presented in Table 1. As expected, no significant differences were found between the 2 groups in terms of matching variables.

3.2. Survival outcomes of different differentiated group

The follow-up time ranged from 8 to 96 months, with an average of 42.6 months (median, 41.0 months) for the well/moderately differentiated group and 41.1 months (median, 38.0 months) for the poorly differentiated group. The patient outcomes at follow-up by differentiation are presented in Table 2. For well/moderately differentiated HPSCC, 37 out of the 102 patients died due to all causes and 29 died because of the disease, while for poorly differentiated HPSCC, 63 out of the 102 patients died due to all causes and 55 died from the disease.

Given the different degrees of differentiation, patients with well/moderately differentiated HPSCC had better 3- and 5-year OS rates than those with poorly differentiated HPSCC (71.7% vs 60.1% for 3-year; 54.7% vs 31.7% for 5-year). Similar results were found for DSS (78.0% vs 65.6% for 3-year; 61.6% vs 36.3% for 5-year) between the 2 groups. Furthermore, the DSS and OS curves in the well/moderately differentiated and poorly differentiated groups are presented in Figure 1. DSS and OS were significantly different between the well/moderately differentiated and poorly differentiated groups (P = .003, P = .001, and P = .006, respectively).

3.3. Matched-pair analysis

In the current matched-pair study, each pair of patients was classified according to the pattern of study events. The concordant was defined as a pair of patients who experienced the same events; in contrast, the discordant was defined as 1 patient of a pair experiencing an event, but the other did not.

According to this definition, in the current study, there were 32 concordant pairs in which both the well/moderately differentiated and poorly differentiated patients died, 31 discordant pairs in which the poorly differentiated patients died but the well/moderately differentiated did not, and 5 discordant pairs

Table 1

Matched patient characteristics.

	WMDG		PDG	
Matched variables	**No. of patients**	**%**	**No. of patients**	**%**
Age (y)				
Mean	57.8 ± 8.0		58.8 ± 8.0	
Median	58.0		61.0	
Range	40–73		37–72	
Sex				
Male	87	85.3	87	85.3
Female	15	14.7	15	14.7
Adult comorbidity score				
None and mild	95	93.1	95	93.1
Moderate and severe	7	6.9	7	6.9
Smoking status				
Smokers	84	82.4	84	82.4
Nonsmokers	18	17.6	18	17.6
Alcohol use				
Drinker	81	79.4	81	79.4
Non-drinker	21	20.6	21	20.6
Primary tumor site				
Pyriform sinus	71	69.6	71	69.6
Postcricoid region	19	18.6	19	18.6
Posterior wall of hypopharynx	12	11.8	12	11.8
Overall stage				
I/II	21	20.6	21	20.6
III/IV	81	79.4	81	79.4
Therapeutic strategies				
Primary surgery*	68	66.7	68	66.7
Primary (chemo)radiation†	34	33.3	34	33.3

PDG = poorly differentiated group, WMDG = well/moderately differentiated group.

*Primary surgery, therapeutic strategies including surgery alone, surgery with radiotherapy or chemoradiotherapy, and introduction chemotherapy followed by surgery.

†Primary (chemo)radiation, therapeutic strategies including definitive radiotherapy, concurrent chemoradiotherapy, and introduction chemotherapy followed by radiotherapy or chemoradiotherapy.

Table 2

Follow-up outcomes by differentiation.

	WMDG		PDG	
Vital status at follow-up	**No. of patients**	**%**	**No. of patients**	**%**
Death, all causes				
No	65	63.7	39	38.2
Yes	37	36.3	63	61.8
Death, owing to disease				
No	73	71.6	47	46.1
Yes	29	28.4	55	53.9

PDG = poorly differentiated group, WMDG = well/moderately differentiated group.

in which the well/moderately differentiated patients died but the poorly differentiated patients did not. Worse differentiation was found to be associated with a significantly reduced risk of overall death (hazard risk [HR], 0.57; 95% confidence interval [CI], 0.38–0.86; P = .007). Multivariable analysis was performed to further adjust for factors that significantly affect prognosis. The well/moderately differentiated patients showed an approximately 49% reduced risk of overall death compared with the poorly differentiated patients after multivariate adjustment (adjusted hazard ratio [aHR], 0.51; 95% CI, 0.34–0.78; P = .002; Table 3). Other factors affected OS after multivariate adjustment included TNM stage (aHR, 6.378; 95% CI, 3.02–13.5; P < .001) and primary tumor site (aHR, 1.38; 95% CI, 1.03–1.84; P = .03).

Similarly, both the well/moderately differentiated and poorly differentiated patients died due to HPSCC in 28 concordant pairs. While the poorly differentiated patients died from the disease, the well/moderately differentiated patients did not in 27 discordant pairs, and the well/moderately differentiated patients died from the disease and the poorly differentiated patients did not in 1 discordant pair. Statistically significant reduction in risk of death owing to disease was found (HR, 0.51; 95% CI, 0.33–0.80; P = .003). After fully adjusting for other important confounders, multivariate analysis showed that the risk of death due to disease was reduced by approximately 56% in the well/moderately differentiated group (aHR, 0.44; 95% CI, 0.28–0.69; P < .001; Table 3). Other factors affected OS after multivariate adjustment included TNM stage (aHR, 1.57; 95% CI, 1.18–2.10; P = .002) and primary tumor site (aHR, 1.43; 95% CI, 1.04–1.98; P = .03).

3.4. Survival outcomes of differentiations stratified by overall stage

Survival outcomes were also compared based on the overall stage (stage I/II and stage III/IV). Figure 2 presents the DSS and OS curves among the 4 groups of patients with different degrees of differentiation and disease stage (well/moderately differentiated with stage I/II, poorly differentiated with stage I/II, well/moderately differentiated with stage III/IV, and poorly differentiated with stage III/IV). For patients with stage III/IV disease, significant differences in DSS and OS were found between the well/moderately differentiated and poorly differentiated groups (P < .001 for 2 aspects). For patients with stage I/II disease, however, no differences in DSS and OS were found between the well/moderately differentiated and poorly differentiated groups (P = .801 and P = .782, respectively).

4. Discussion

No previous studies have reported matched-pair analyses to evaluate the effect of differentiation on survival in patients with HPSCC. In the current study, 102 poorly differentiated HPSCC cases were matched to 102 well/moderately differentiated cases

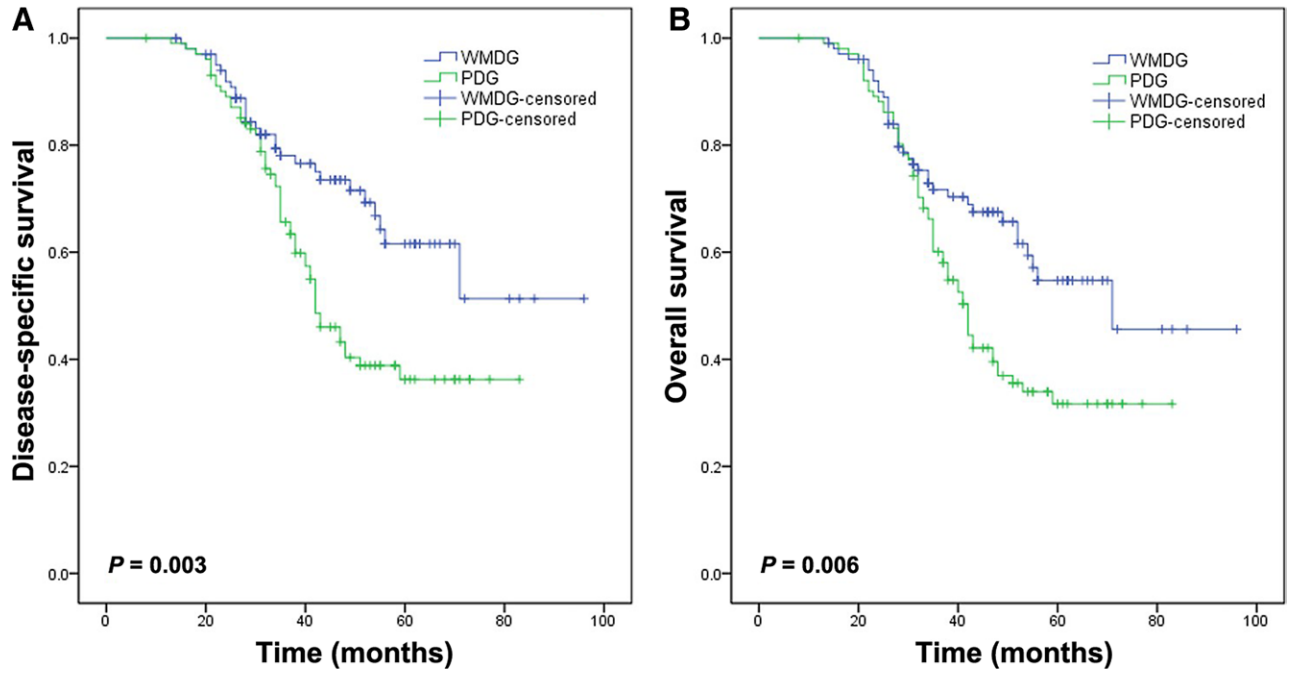

Figure 1. Survival outcomes by different differentiation groups. (A) Comparison of the Kaplan-Meier survival curves on disease-specific survival in the WMDG and the PDG (P = .003); (B) Comparison of the Kaplan-Meier survival curves on overall survival in the WMDG and PDG (P = .006). Censoring is indicated by tick marks. PDG = poorly differentiation group, WMDG = well/moderately differentiation group.

Table 3

Risk associated with differentiation.

	Risk, WMDG vs PDG			Risk after regression for cancer-associated variables*		
Matched-pair analysis	**HRs**	***P* value**	**95% CI**	**aHRs**	***P* value**	**95% CI**
OS	0.57	.007	0.38–0.86	0.51	.002	0.34–0.78
DSS	0.51	.003	0.33–0.80	0.44	<.001	0.28–0.69

aHR = adjusted hazard ratio, CI = confidence interval, HR = hazard ratio, PDG = poorly differentiated group, WMDG = well/moderately differentiated group.

*Adjusted for cancer-associated variables: age, sex, adult comorbidity score, smoking status, alcohol use, primary tumor site, overall stage, and therapeutic strategies.

using the matching variables of age, sex, disease stage, smoking and alcohol status, and treatment. The results showed that worse differentiation was significantly associated with a higher risk of HPSCC death. These findings suggest that differentiation may affect the survival of patients with HPSCC.

A previous study including 62 cases of HPSCC showed that the survival rate of patients with well-differentiated tumors was better than that of patients with poorly and moderately differentiated tumors, and tumor differentiation (HR = 2.131, P = .030) was an independent predictor of better OS.[6] By analyzing the clinicopathological data of 170 patients with HPSCC, Gang et al[15] found that poor differentiation was an independent risk factor for survival outcomes. These findings are consistent with those of the current study. Although it has been reported that poorly differentiated HPSCC has high malignancy and strong invasive ability, the National Comprehensive Cancer Network Guidelines do not recommend a therapy plan according to pathological differentiation.[16] However, in the current study, multivariate analysis showed that among patients with poorly differentiated HPSCC, those who received treatment including chemoradiation tended to have a better prognosis than those without chemoradiation, although the difference was not statistically significant (P = .08). This finding suggests that poorly differentiation might be another adverse feature of HPSCC, and patients with poorly differentiated tumors should be considered for chemoradiation to a more active extent for further improvement of the prognosis.

In this study, we found that differentiation was an important factor in the survival outcomes of patients with HPSCC, especially for those with advanced tumors (stage III/IV). However, the current American Joint Committee on Cancer TNM staging system (8th ed, 2017) was developed for differentiation-unrelated HPSCC. Further studies with larger sample sizes in multiple centers are necessary to verify our findings, and a new staging system might be needed to adequately predict the survival outcomes of patients with differentiation-related HPSCC.

This study had several limitations. The possibility of the bias for patient selection was one of the limitations because it was a single-center hospital-based retrospective study. In addition, the relatively small sample size (102 pairs) was also a potential limitation. Nevertheless, the follow-up of a minimum of 3 years or until death for all participants may offset this limitation to some extent. Finally, other potentially important data, such as gastroesophageal reflux, passive smoking, the intensity and duration of drinking and smoking and family cancer history were not included in this study. These issues remain to be collected in future larger studies to further validate the current findings.

5. Conclusion

Patients with poorly differentiated HPSCC had worse DSS and OS compared to those with well/moderately differentiated tumors after being matched by age, sex, smoking and alcohol use, comorbidity score, and treatment strategies. Tumor differentiation might serve as a prognostic factor for patients with HPSCC. Considerable importance should be attached to the therapeutic decision of poorly differentiated HPSCC.

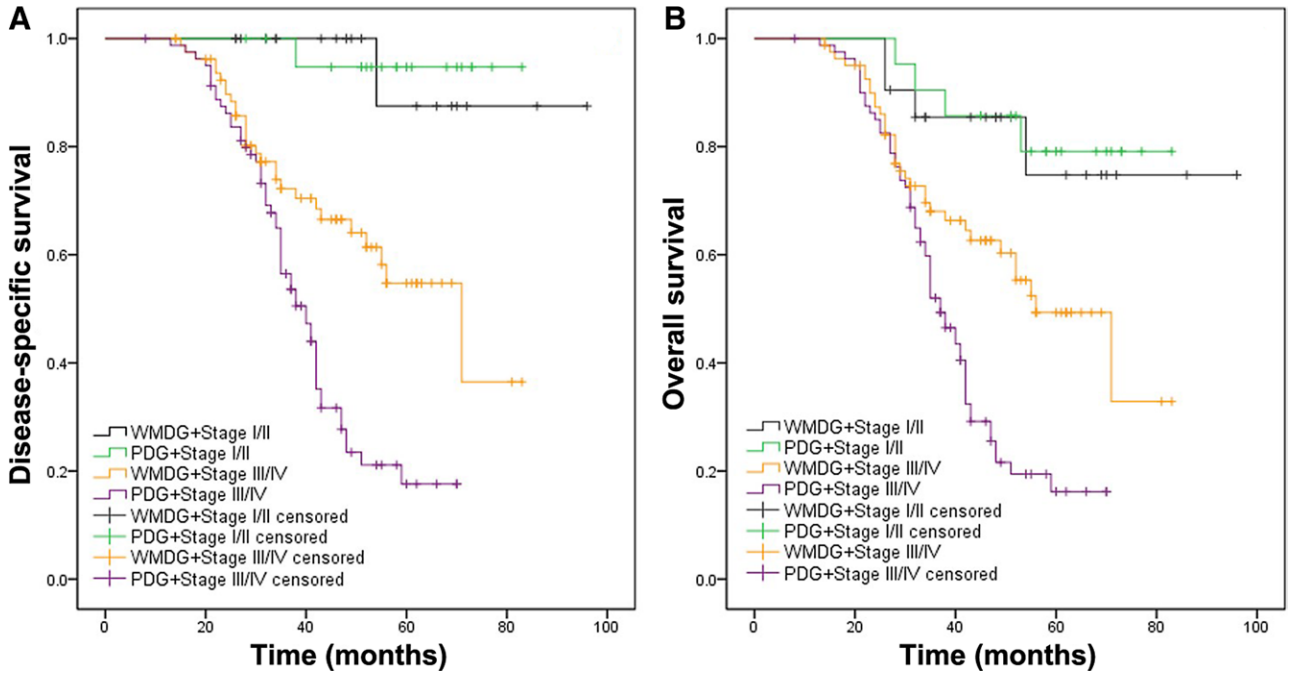

Figure 2. DSS (A) and OS (B) by different differentiation and stage groups (WMDG with stage I/II, PDG with stage I/II, WMDG with stage III/IV and PDG with stage III/IV). No differences of DSS and OS were found between WMDG with stage I/II and PDG with stage I/II (P = .801 and P = .782, respectively). Significant differences of DSS and OS were found between WMDG with stage III/IV and PDG with stage III/IV (P < .001 for both). Censoring is indicated by tick marks. DSS = disease-specific survival, OS = overall survival, PDG = poorly differentiated group, WMDG = well/moderately differentiated group.

Authors' contributions

XX and XC conceived the study. XX, YL, YZ, XZ and WD acquired the data. XX, YL and YZ analyzed and interpreted the data. XX and YL prepared the manuscript. All authors read and approved the final manuscript for publication.

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