CANCER DIAGNOSIS & PROGNOSIS
4: 789-796 (2024) doi: 10.21873/cdp.10397

Prediction of Treatment Response Based on Nutritional Status and Tumor Immunity in Oropharyngeal Cancer Patients Treated With Chemoradiotherapy

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Abstract. *Background/Aim: Radiotherapy (RT) for advanced oropharyngeal cancer (OPC) is effective, especially when combined with chemotherapy (CRT). However, its success can vary depending on factors, such as tumor stage, HPV infection (p16 status), and the patient's nutritional and immune status. This study examined the controlling nutritional status (CONUT) score and tumor immunity as predictive factors for treatment outcomes in OPC, aiming to develop a personalized risk score. Patients and Methods: A retrospective analysis was conducted on 84 patients with OPC treated with definitive RT or CRT, and survival outcomes were compared based on various factors, including BMI, CONUT score, CD8 expression, and HLA class II expression. Results: We observed better overall survival (OS) rates in CD8-positive patients and those with higher HLA class II expression. The univariate analysis identified stage, p16 status, BMI, CONUT score, and CD8 expression as significantly associated with OS. In multivariate analysis, stage, BMI, and CONUT score remained significant predictors of OS. A risk scoring system was developed based on stage, p16 status, BMI, CONUT score, and CD8 expression. Patients were categorized into low-risk and high-risk groups, with significantly better survival in the low-risk group. Conclusion: A combined risk score incorporating clinical, nutritional, and immune factors can improve the prediction of treatment outcomes for OPC patients. This risk stratification may enable personalized treatment plans and improve OS rates.*

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Key Words: Oropharyngeal cancer, radiotherapy, chemotherapy, CONUT score, body mass index, CD8, Forkhead box P3, Human leukocyte antigen class II.

Radiotherapy (RT) is an effective treatment for advanced oropharyngeal cancer (OPC), especially when combined with chemotherapy if surgical treatment is not feasible, preserving functions, such as speech and swallowing (1). However, the effectiveness of radiotherapy can vary among individuals. Factors such as tumor stage, status of HPV infection (2), the patient's nutritional status, and tumor immunity have all been associated with treatment outcomes (3, 4). Namely, a poor nutritional status may increase the risk of infections and complications during treatment, making it difficult to complete the course of treatment. Nutritional status also has been associated with tumor immunity, and it has been reported that an individual's immune system function can affect their response to treatment (5-7). Therefore, assessment of nutritional status and tumor immunity prior to treatment is an important prognostic factor in predicting outcome of radiation therapy for oropharyngeal cancer.

The controlling nutritional status (CONUT) score was developed as a scoring system to evaluate the nutritional status of patients using three indices: serum albumin, total lymphocyte count, and total cholesterol level (8), there have been reports of the prognostic utility of the CONUT score in the surgical treatment of several types of cancers (9-11). However, little has been reported on its usefulness in predicting the outcome of radiotherapy. Therefore, this study examined the pretreatment nutritional status and factors

involved in tumor immunity (especially tumor-infiltrating CD8 or FoxP3-positive T lymphocytes) in patients with OPC undergoing chemoradiotherapy (CRT) at our institution. The goal was to develop a risk score to identify patients who would benefit from radiation therapy in combination with these factors.

Patients and Methods

Patients. This retrospective study was approved by the Ethics Committee of Sapporo Medical University Hospital (No. 312-168). All patients provided opt-out consent for the use of their clinical information and biopsy specimens. The study included 84 patients who underwent definitive RT, CRT, or bioradiotherapy (BRT) at our institution between May 2005 and December 2022, and who met the following criteria: [1] pathologically confirmed squamous cell carcinoma of the oropharynx; [2] received a radiation dose of 66 Gy or higher; [3] availability of sufficient clinical data, including clinical outcomes; and [4] availability of archived biopsy specimens (formalin-fixed paraffin-embedded tissue).

The diagnostic workup included visual inspection, palpation, fiberscopy, and head and neck imaging using computed tomography (CT) and/or magnetic resonance imaging (MRI). Clinical tumor staging was determined according to the American Joint Committee on Cancer (AJCC) TNM staging system, version 8 (12). The baseline characteristics of patients are shown in Table I. The CONUT score was calculated to assess nutritional status (8). Briefly, nutritional status was evaluated based on serum albumin, lymphocyte count, and total cholesterol levels, with a total score ranging from 0 to 12. A score below 3 was defined as good nutritional status, while a score above 3 indicated poor nutritional status.

Table I. *Patients characteristics*.

		N=84	%
	Median age at diagnosis	70	
	Range	40-90	
Sex	Male	73	86.9
	Female	11	13.1
PS	0	65	77.4
	≥1	19	22.6
Primary anatomic site	Tonsil	56	66.7
	Base of tongue	19	22.6
	Upper wall	7	8.3
	Posterior wall	2	2.4
p16 status	Positive	43	51.2
	Negative	41	48.8
Smoking status	Never smoker	17	20.2
	Current/Ex-smoker	67	79.8
Alcohol status	Non-drinker	23	27.4
	Current/Ex-drinker	61	72.6
TNM stage	I	21	25.0
	II	21	25.0
	III	17	20.2
	IV	25	29.8
Body Mass Index	<22	47	56.0
	≥22	37	44.0
CONUT score	<3	61	72.6
	≥3	23	27.4

PS: Performance status; CONUT: controlling nutritional status.

Treatment. All patients were treated with curative intent. The radiation dose ranged from 66 Gy to 72 Gy in standard fractionation. Radiation therapy was delivered using 4-MV or 6-MV X-rays. Thirty-four patients were treated with three-dimensional conformal radiation therapy (3D-CRT), while fifty patients received intensity-modulated radiation therapy (IMRT). Among those who underwent chemotherapy, seven patients received induction chemotherapy prior to RT, and sixty-two were treated with concurrent CRT. The chemotherapy agents used were cisplatin, 5-FU, or S-1, either as single agents or in combination. Five patients underwent BRT with cetuximab. Seventeen patients received RT alone.

Immunohistochemical staining. Immunohistochemical staining was carried out using the methods described in a previous study (13). In brief, formalin-fixed, paraffin-embedded specimens from pretreatment endoscopic biopsy were sliced into 3-mm thick sections and mounted on glass slides. Primary antibodies against the following antigens were used: p16 (Ventana Medical Systems, Tucson, AZ, USA), CD8 (clone C8/144B; Dako, Glostrup, Denmark), FoxP3 (clone 236A/E7; Abcam, Cambridge, UK), and HLA class II [clone EPR3692 (ab92511); Abcam]. Positive p16 expression was defined as strong and diffuse nuclear and cytoplasmic staining in 70% or more of the tumor cells (2). The number of CD8- and FoxP3-positive cells was manually counted at 400× magnification under a microscope. In this study, CD8 positivity was defined as more than 270 positive cells, and FoxP3 positivity was defined as more than 60 positive cells. HLA class II positivity in the tumor was evaluated across the entire slide, and a tumor was considered HLA class II positive if the expression was 30% or higher. The immunohistochemical staining results were evaluated by two researchers (including one pathologist) who were blinded to treatment outcomes. Representative images are shown in Figure 1.

Follow-up schedule. The median follow-up duration was 54 months (range=3-191 months). Post-treatment evaluations included physical examinations, laboratory tests for tumor markers, fiberscopy, CT and/or MRI, and positron emission tomography/CT when necessary. The follow-up intervals were 1 to 2 months during the first and second years after treatment, and 3 to 6 months thereafter. The overall survival (OS) rate was calculated from the date radiation therapy ended to the date of death from any cause or the date of the last follow-up visit. The progression-free survival (PFS) rate was calculated from the date radiation therapy ended to the date of death from any cause, the date of recurrence detection, or the date of the last follow-up visit. The cut-off date for this analysis was February 2024.

Statistical analysis. The OS and PFS curves were estimated using the Kaplan-Meier method, and the log-rank test was used to compare survival curves. Comparisons between clinical and demographic characteristics with immunostaining were performed using Fisher's exact test. The Cox proportional hazards model was used for univariate and multivariate analyses. Multivariate analyses were conducted on variables with a p-value of less than 0.05 in the univariate analysis. All values were two-sided, with a significance level set at 0.05. All statistical analyses were performed using EZR software, version 1.33 (14).

Results

At the time of analysis, 21 of the 84 patients had died of their primary disease and 18 had died of other diseases, and the 5-year OS rate for all patients was 57.9%. The 5-year OS rates according to stage were 89.1% for Stage I, 72.2% for Stage II, 35.7% for Stage III, and 24.6% for Stage IV (Figure 2). The 5-year PFS rates by Stage were 66.7% for Stage I, 62.4% for Stage II, 37.5% for Stage III, and 9.2% for Stage IV.

Table II shows the association between immunostaining for proteins involved in tumor immunity and clinical factors and nutritional status. When comparing the expression of CD8-positive cells infiltrating around the tumor with clinical factors, the CD8-positive group had a significantly higher p16-positive rate (82.1% *vs*. 35.7%, $p<0.001$) and a higher percentage of patients in Stages I-III (89.3% *vs*. 60.7%, $p=0.024$). There was no clear correlation between the expression of FoxP3-positive cells infiltrating around the tumor and any clinical factors. In the group with positive HLA class II expression on the tumor surface, p16 positivity was significantly higher (75.9% *vs*. 38.2%, $p=0.001$), and the percentage of non-drinkers was higher (44.8% *vs*. 18.2%, $p=0.019$).

Figure 3A-C shows the OS rate stratified by the positivity of CD8, FoxP3, and HLA class II. Significantly better OS was observed in the CD8-positive group (Figure 3A; 5y-OS 78% *vs*. 42%, $p=0.019$); FoxP3 showed no significant difference between the positive and negative groups (Figure 3B; 5y-OS 58% *vs*. 56%, $p=0.667$). HLA class II showed a trend toward better OS in the positive group (Figure 3C; 5y-OS 70% *vs*. 46%, $p=0.082$).

According to the univariate results presented in Table III, the factors significantly associated with OS were Stage (HR=3.608, $p<0.001$), p16 status (HR=2.736, $p=0.003$), Body mass index (BMI) (HR=1.986, $p=0.044$), CONUT score (HR=2.279, $p=0.017$), and CD8 expression (HR=2.445, $p=0.019$), whereas other factors were not significantly associated with OS. In the multivariate analysis, Stage, BMI, and CONUT score were identified as significant factors associated with OS ($p=0.037$, $p=0.042$, and $p=0.012$).

Finally, a combined risk score was generated by summing the status of Stage, p16, BMI, CONUT score, and CD8 expression as follows: Risk Score=(Stage IV)*1+(p16 negative)*2+(BMI<22)*2+(CONUT≥3)*1+(CD8-negative)*1.

The combined risk score ranged from 0 to 7. The low-risk group was defined as having a score of 0-2, while the high-risk group was defined as having a score of 3-7. OS was significantly better in the low-risk group compared to the high-risk group ($p<0.001$; 5-year OS: 80.0% *vs*. 36.5%; Figure 4). Figure 5 shows the predictive accuracy using Receiver Operating Characteristic (ROC) analysis: the area under the curve (AUC) was 0.696 for clinical factors, such as stage and p16 status alone. However, when nutritional and tumor immune status factors—such as BMI, CONUT score, and CD8—were added, the AUC increased to 0.765, indicating an improvement in predictive accuracy with borderline significance ($p=0.079$).

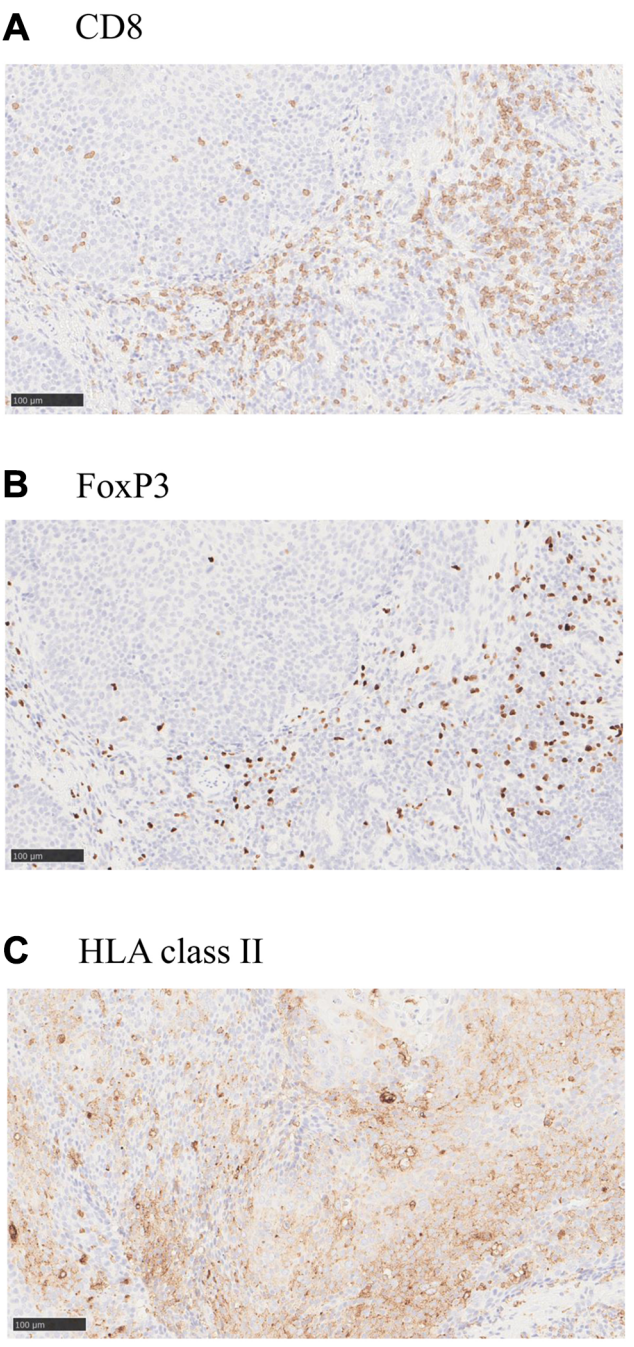

Figure 1. *Representative images of immunohistochemically stained biopsy specimens with positive cases. (A) CD8 positive lymphocytes infiltrating around tumor nest, (B) FoxP3 positive lymphocytes infiltrating around tumor nest, (C) HLA class II positive tumor cells.*

Table II. *Association between clinical parameters and immune expression levels.*

	Expression of CD8			Expression of FoxP3			Expression of HLA class II		
	Positive	Negative	*p*-Value	Positive	Negative	*p*-Value	Positive	Negative	*p*-Value
Age									
≥65	18	10	0.629	22	35	1.000	17	40	0.224
<65	10	17		11	16		12	15	
BMI									
<22	15	32	0.818	28	18	1.000	14	33	0.359
≥22	13	24		22	29		15	22	
p16 status									
Positive	23	20	**<0.001**	20	23	0.186	22	21	**0.001**
Negative	5	36		13	28		7	34	
Stage									
I-III	25	34	**0.024**	22	37	0.629	24	35	0.083
IV	3	22		11	14		5	20	
Smoking status									
Never smoker	4	13	0.401	7	10	1.000	5	12	0.778
Current/Ex-smoker	24	43		26	41		24	43	
Alcohol status									
Non-drinker	8	15	1.000	12	11	0.210	13	10	**0.019**
Current/Ex-drinker	20	41		21	40		16	45	
CONUT score									
≥3	6	17	0.446	8	15	0.803	7	16	0.798
<3	22	39		25	36		22	39	

BMI: Body mass index; CONUT: controlling nutritional status. Statistically significant *p*-values are shown in bold.

Discussion

The standard curative treatment for OPC is surgical resection or RT combined with chemotherapy (1, 15). However, the functional deficit caused by surgery leads to a decrease in quality of life (16), since the location of the oropharynx is involved in various functions, such as mastication, swallowing, and speech (16). On the other hand, CRT may be an effective treatment that can preserve these functions, but the outcome is not always better than surgery and sometimes causes a certain range of late adverse events (17). To solve this problem, we focused on the relationship between nutritional status, tumor immunity, and the outcomes from RT.

The results shown in Table III indicate that stage, p16 status, BMI, CONUT score, and CD8-positive cell infiltration were significant factors associated with OS in univariate analysis, and stage, BMI, and CONUT score remained significant factors in multivariate analysis. A risk score combining these factors was developed to effectively differentiate between groups with higher and lower responses to CRT.

Previous studies have reported that several nutritional indices are associated with treatment outcomes in head and neck cancer (10, 18-21). Oh *et al*. have evaluated the nutritional risk index (NRI) in patients undergoing radical CRT for head and neck cancer and reported that CRT can significantly reduce nutritional scores and that pretreatment

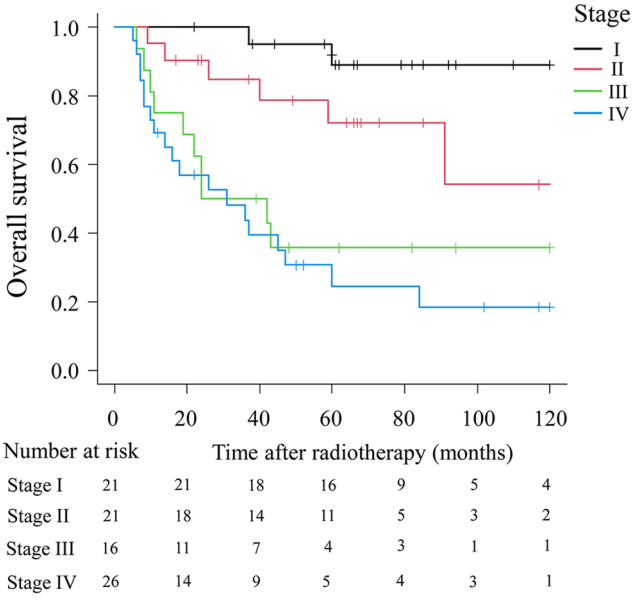

Figure 2. *Overall survival according to tumor stage.*

NRI risk categories were associated with OS and treatment-related complications, indicating that the NRI may be a useful prognostic factor (18). Brewczyński *et al*. have examined the impact of CRT in oropharyngeal cancer

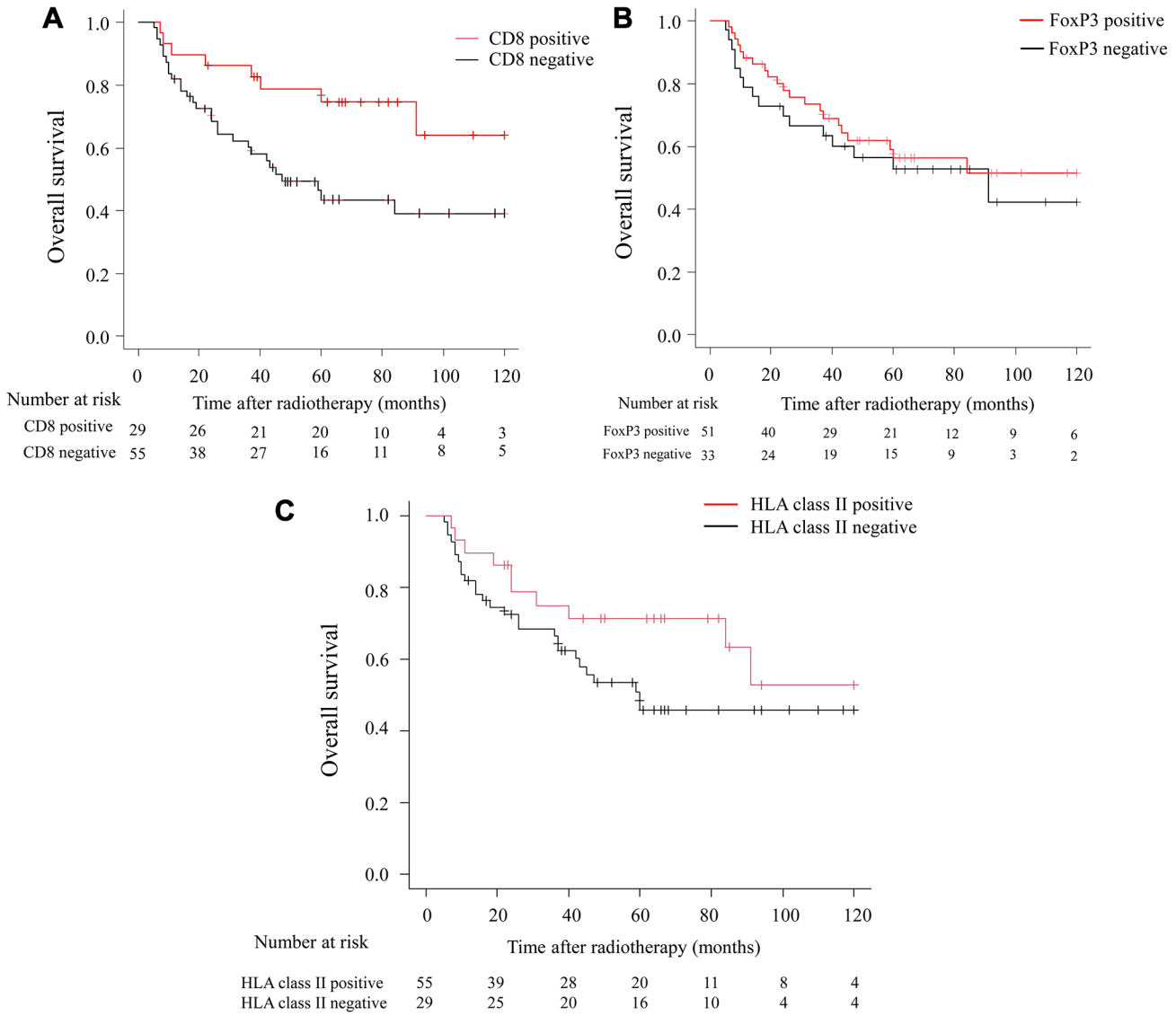

Figure 3. *Overall survival according to the expression of proteins. (A) CD8 positive vs. negative (p=0.019); (B) FoxP3 positive vs. negative (p=0.667); (C) HLA class II positive vs. negative (p=0.082).*

patients and reported that nutritional status had a strong impact on OS and PFS and concluded that OPC patients require adequate nutritional support during CRT (20). Furthermore, Matsuura *et al*. have reported that PNI (Prognostic Nutritional Index), one of the nutritional markers is useful in predicting the response to immunotherapy for advanced head and neck cancer (21). Our results are consistent with these studies, suggesting that the CONUT score and BMI, both of which reflect nutritional status, are significant predicting factors in CRT for OPC.

As shown in Table II, there was a significant correlation between p16 status, namely HPV infection, and CD8 positivity. This is consistent with our previous study (7), suggesting that p16-positive tumors caused by HPV infection might induce a more active host anti-tumor immune response than p16-negative tumors, thus leading to higher CD8 infiltration. Several studies on tumor immunity have also been reported showing that tumor-infiltrating lymphocytes of cytotoxic T cells are associated with favorable RT effects (7, 22-24). Haist *et al*. have investigated the function of CD8+ T cells in the tumor microenvironment in OPC patients and have reported that p16 expression correlates with CD8+ T cell infiltration around the tumor and associated with better CRT efficacy and survival (22). Kawaguchi *et al*. have also reported that in patients with OPC and nasopharyngeal cancer, a higher

Table III. *Univariate and multivariate analysis of clinical, nutritional and immunological factors associated with overall survival.*

		Univariate analysis				Multivariate analysis			
Variables		HR	95%CI	*p*-Value	Poor diagnosis	HR	95%CI	*p*-Value	Poor diagnosis
Stage	I-III *vs*. IV	3.274	1.71-6.271	**<0.001**	IV	2.149	0.904-5.109	0.083	
p16 status	Negative *vs*. positive	0.366	0.187-0.714	**0.003**	Negative	0.546	0.210-1.416	0.213	
Age	<65 y *vs*. ≥65 y	1.805	0.856-3.806	0.121					
BMI	<22 *vs*. ≥22	1.986	1.019-3.872	**0.044**	<22	2.073	1.032-4.168	**0.041**	<22
Drinking	Non-drinker *vs*. Current/ Ex-drinker	0.819	0.411-1.628	0.567					
Smoking	Never smoker *vs*. Current/ Ex-smoker	1.286	0.587-2.815	0.529					
CONUT score	<3 *vs*. ≥3	2.279	1.162-4.47	**0.017**	≥3	2.450	1.213-4.947	**0.012**	≥3
CD8	Low *vs*. high	2.445	1.153-5.184	**0.019**	low	1.262	0.533-2.989	0.596	
FoxP3	Low *vs*. high	0.869	0.459-1.647	0.667					
HLA class II	Low *vs*. high	0.526	0.255-1.085	0.082					

BMI: Body Mass Index; CONUT: controlling nutritional status; HR: hazard ratio; CI: confidence interval. Statistically significant *p*-values are shown in bold.

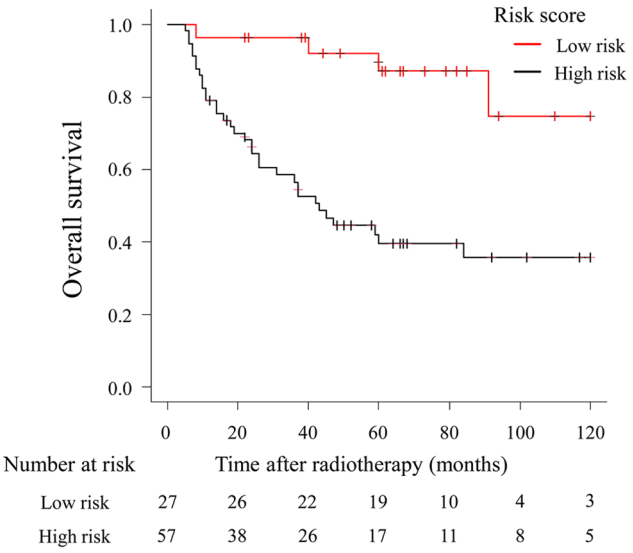

Figure 4. *Overall survival stratified by the combined risk score; low-risk group (score 0-2) vs. high-risk group (score 3-7) (p<0.001).*

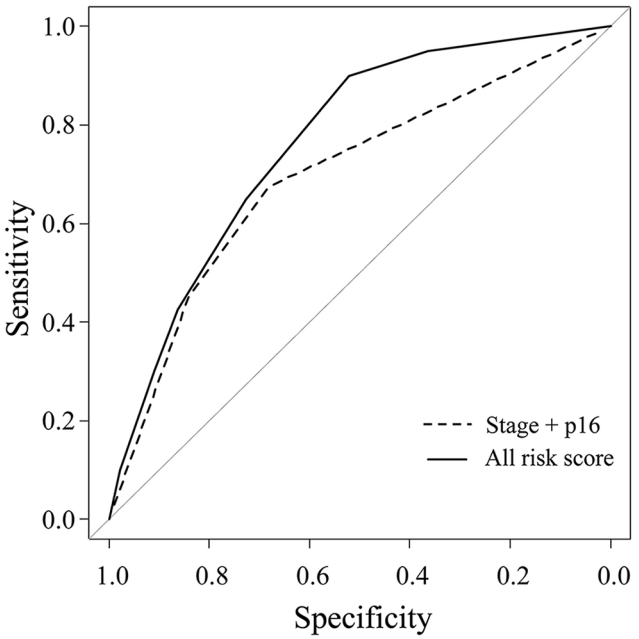

Figure 5. *The ROC curves of prediction for overall survival. A dotted line indicates ROC curve for combinations of clinical parameters (Stage and p16 status). A solid line shows ROC curve for combinations of all parameters (Stage, p16 status, BMI, CONUT score, and CD8 positivity).*

density of CD8+ tumor-infiltrating lymphocytes and increased expression of PD-L1 were associated with a better survival. Notably a higher CD8+ TIL density was a strong predictor of improved PFS and OS (23). Similar to these studies, our results suggest that factors related to tumor immunity, such as CD8+ cell infiltration, are associated with OS, and that the pretreatment tumor immunity affects the response to CRT.

As shown in Figure 4 and Figure 5, a risk score combining the significant factors found in the univariate analysis appeared to better predict treatment outcomes in OPC patients. There have been several attempts to distinguish outcomes by assigning risk scores (25). Lo *et al*. have identified low pretreatment hemoglobin and high systemic immunoinflammatory index levels as important indicators for predicting risk of death within one year after CRT for OPC and have concluded that nomograms created on this basis are useful for determining treatment strategy. Similarly, our study is based on relatively simple clinical data, such as Stage, p16 status, BMI, CONUT score, and CD8+ infiltration, and therefore, our scoring was relatively simple and clinically accessible.

Important limitations of this study were the relatively small sample size and the heterogeneity of patient profiles and treatments, which are drawbacks of retrospective studies and require further study for validation for more accurate prediction. Another limitation was that protein expression related to tumor immunity, such as CD8-positive cell infiltration and HLA expression, could vary by biopsy site and require evaluation by a skilled pathologist. However, our recent study has reported the usefulness of the Qupath automated measurement software for the evaluation of immunostained specimens (26), and its introduction may improve the accuracy of risk score evaluation.

In conclusion, this study proposed a combined risk scoring system based on an analysis of the association of clinical, nutritional, and immune factors with the outcome of patients undergoing radical CRT for OPC. Stratifying patients using this risk score may enable personalized treatment plans, helping to determine the optimal therapy and potentially improving outcomes for OPC.

Funding

This work was supported by JSPS KAKENHI Grant Number 23K14923, 23K07161 and 24K10913.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in relation to this study.

Authors' Contributions

Conceptualization, M.K. and J.K.; Methodology, M.S.; Software, S.M.; Validation, T.H., T.T. and Y.F.; Formal Analysis, S.M.; Investigation, M.S. and J.K; Data Curation, M.S., T.K., Y.H., Y.I., R.O., A.O., A.A, Y.T., and T.T.; Writing – Original Draft Preparation, M.S.; Writing – Review & Editing, M.S. and K.M.; Visualization, T.G. and R.O.; Supervision, T.T. and K.S.; Project Administration, K.S.; Funding Acquisition, M.S.

References

1 Pignon JP, le Maître A, Maillard E, Bourhis J, MACH-NC Collaborative Group: Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients. Radiother Oncol 92(1): 4-14, 2009. DOI: 10.1016/j.radonc.2009.04.014

2 Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, Westra WH, Chung CH, Jordan RC, Lu C, Kim H, Axelrod R, Silverman CC, Redmond KP, Gillison ML: Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 363(1): 24-35, 2010. DOI: 10.1056/NEJMoa0912217

3 Qiu J, Yang J, Yu Y, Wang Z, Lin H, Ke D, Zheng H, Li J, Yao Q: Prognostic value of pre-therapeutic nutritional risk factors in elderly patients with locally advanced esophageal squamous cell carcinoma receiving definitive chemoradiotherapy or radiotherapy. BMC Cancer 23(1): 597, 2023. DOI: 10.1186/s12885-023-11044-5

4 Yeh P, Chang CM, Liao LJ, Wu CY, Hsieh CH, Shueng PW, Cheng PW, Lo WC: A predictive survival model for patients with stage IV oropharyngeal squamous cell carcinoma treated with chemoradiation. Eur Arch Otorhinolaryngol 281(1): 369-377, 2024. DOI: 10.1007/s00405-023-08187-3

5 Ruangritchankul K, Sandison A, Warburton F, Guerrero-Urbano T, Reis Ferreira M, Lei M, Thavaraj S: Clinical evaluation of tumour-infiltrating lymphocytes as a prognostic factor in patients with human papillomavirus-associated oropharyngeal squamous cell carcinoma. Histopathology 75(1): 146-150, 2019. DOI: 10.1111/his.13873

6 Furgiuele S, Descamps G, Lechien JR, Dequanter D, Journe F, Saussez S: Immunoscore combining CD8, FoxP3, and CD68-positive cells density and distribution predicts the prognosis of head and neck cancer patients. Cells 11(13): 2050, 2022. DOI: 10.3390/cells11132050

7 Fukushima Y, Someya M, Nakata K, Hori M, Kitagawa M, Hasegawa T, Tsuchiya T, Gocho T, Ikeda H, Hirohashi Y, Torigoe T, Sugita S, Hasegawa T, Himi T, Sakata KI: Influence of PD-L1 expression in immune cells on the response to radiation therapy in patients with oropharyngeal squamous cell carcinoma. Radiother Oncol 129(2): 409-414, 2018. DOI: 10.1016/j.radonc.2018.08.023

8 Ignacio de Ulíbarri J, González-Madroño A, de Villar NG, González P, González B, Mancha A, Rodríguez F, Fernández G: CONUT: a tool for controlling nutritional status. First validation in a hospital population. Nutr Hosp 20: 38-45, 2005.

9 Kheirouri S, Alizadeh M: Prognostic potential of the preoperative controlling nutritional status (CONUT) score in predicting survival of patients with cancer: a systematic review. Adv Nutr 12(1): 234-250, 2021. DOI: 10.1093/advances/nmaa102

10 Wang Y, Qian C: Prognostic and clinicopathological value of the controlling nutritional status (CONUT) score in patients with head and neck cancer: a meta-analysis. World J Surg Oncol 22(1): 223, 2024. DOI: 10.1186/s12957-024-03505-3

11 Cozzani F, Ricchiuto M, Virgilio E, Viani L, Rossini M, Pedrazzi G, Del Rio P: The Controlling Nutritional Status (CONUT) score predicts post-operatory risks and prognosis in patients with surgically treated colon cancer: a retrospective study. Anticancer Res 44(9): 3955-3964, 2024. DOI: 10.21873/anticanres.17224

12 Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR,

Sullivan DC: AJCC Cancer Staging Manual. 8th Edition. Springer International Publishing, 2018.
13 Sakata K, Matsumoto Y, Tauchi H, Satoh M, Oouchi A, Nagakura H, Koito K, Hosoi Y, Suzuki N, Komatsu K, Hareyama M: Expression of genes involved in repair of DNA double-strand breaks in normal and tumor tissues. Int J Radiat Oncol Biol Phys 49(1): 161-167, 2001. DOI: 10.1016/s0360-3016(00)01352-3
14 Kanda Y: Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 48(3): 452-458, 2013. DOI: 10.1038/bmt.2012.244
15 NCCN Guidelines Version 4.2024 Head and Neck Cancers. National Comprehensive Cancer Network. National Comprehensive Cancer Network. Available at: http://www.nccn.org/ [Last accessed on September 1, 2024]
16 Cmelak AJ, Li S, Goldwasser MA, Murphy B, Cannon M, Pinto H, Rosenthal DI, Gillison M, Forastiere AA: Phase II trial of chemoradiation for organ preservation in resectable stage III or IV squamous cell carcinomas of the larynx or oropharynx: results of Eastern Cooperative Oncology Group study E2399. J Clin Oncol 25(25): 3971-3977, 2007. DOI: 10.1200/JCO.2007.10.8951
17 Machtay M, Moughan J, Trotti A, Garden AS, Weber RS, Cooper JS, Forastiere A, Ang KK: Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. J Clin Oncol 26(21): 3582-3589, 2008. DOI: 10.1200/JCO.2007.14.8841
18 Oh J, Liu A, Tran E, Berthelet E, Wu J, Olson RA, Chau N, Bowman A, Hamilton SN: Association between nutritional risk index and outcomes for head and neck cancer patients receiving concurrent chemo-radiotherapy. Head Neck 42(9): 2560-2570, 2020. DOI: 10.1002/hed.26315
19 Fanetti G, Polesel J, Fratta E, Muraro E, Lupato V, Alfieri S, Gobitti C, Minatel E, Matrone F, Caroli A, Revelant A, Lionello M, Zammattio Polentin V, Ferretti A, Guerrieri R, Chiovati P, Bertolin A, Giacomarra V, Paoli A, Vaccher E, Sartor G, Steffan A, Franchin G: Prognostic Nutritional Index predicts toxicity in head and neck cancer patients treated with definitive radiotherapy in association with chemotherapy. Nutrients 13(4): 1277, 2021. DOI: 10.3390/nu13041277
20 Brewczyński A, Jabłońska B, Mazurek AM, Mrochem-Kwarciak J, Mrowiec S, Śnietura M, Kentnowski M, Kotylak A, Kołosza Z, Składowski K, Rutkowski T: Analysis of selected nutritional parameters in patients with HPV-related and non-HPV-related oropharyngeal cancer before and after radiotherapy alone or combined with chemotherapy. Cancers (Basel) 14(9): 2335, 2022. DOI: 10.3390/cancers14092335
21 Matsumura S, Kaira K, Kuba K, Inoue H, Hamada M, Yamazaki T, Nakahira M, Ebihara Y: Potential of nutritional markers as predictors after immunotherapy in advanced head and neck squamous cell carcinoma. Anticancer Res 44(9): 4049-4056, 2024. DOI: 10.21873/anticanres.17234
22 Haist M, Kaufmann J, Kur IM, Zimmer S, Grabbe S, Schmidberger H, Weigert A, Mayer A: Response to primary chemoradiotherapy of locally advanced oropharyngeal carcinoma is determined by the degree of cytotoxic T cell infiltration within tumor cell aggregates. Front Immunol 14: 1070203, 2023. DOI: 10.3389/fimmu.2023.1070203
23 Kawaguchi T, Ono T, Sato F, Kawahara A, Kakuma T, Akiba J, Sato K, Chitose SI, Umeno H: CD8+ T cell infiltration predicts chemoradiosensitivity in nasopharyngeal or oropharyngeal cancer. Laryngoscope 131(4): E1179-E1189, 2021. DOI: 10.1002/lary.29097
24 Katano A, Minamitani M, Ohira S, Yamashita H: Curative radiotherapy for oropharyngeal squamous cell carcinoma stratified by p16 status, according to the eighth edition American Joint Committee on Cancer staging manual: a retrospective study. Cancer Diagn Progn 4(2): 117-121, 2024. DOI: 10.21873/cdp.10296
25 Lo WC, Chang CM, Wu CY, Hsieh CH, Shueng PW, Cheng PW, Liao LJ: A predictive model for advanced oropharyngeal cancer patients treated with chemoradiation. BMC Cancer 22(1): 615, 2022. DOI: 10.1186/s12885-022-09732-9
26 Hasegawa T, Someya M, Tsuchiya T, Kitagawa M, Fukushima Y, Gocho T, Mafune S, Okuda R, Kaguchi J, Ohguro A, Kamiyama R, Ashina A, Toshima Y, Hirohashi Y, Torigoe T, Sakata KI: Identification and quantification of radiotherapy-related protein expression in cancer tissues using the Qupath software and prediction of treatment response. In Vivo 38(3): 1470-1476, 2024. DOI: 10.21873/invivo.13593

Received September 6, 2024
Revised September 19, 2024
Accepted September 20, 2024