Clinical significance of pretreatment prognostic nutritional index and lymphocyte-to-monocyte ratio in patients with advanced p16-negative oropharyngeal cancer

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Background. Systemic inflammation and nutrition status both play roles in the survival of cancer patients. It would be valuable to study the effect of prognostic nutritional index (PNI) and lymphocyte-to-monocyte ratio (LMR) on survival in patients with advanced p16-negative oropharyngeal cancer. **Methods.** There were 142 patients who diagnosed advanced p16-negative oropharyngeal cancer between 2008 and 2015 enrolled in this study. All patients received primary treatment with definite concurrent chemoradiotherapy (CCRT). Optimal cutoff values of PNI and LMR were determined by receiver operating characteristic curve for survival prediction. Five-year overall survival (OS), disease-specific survival (DSS), and disease-free survival (DFS) rates for prognostic factors were also estimated. Effects of PNI and LMR on survival were assessed by Cox regression model with adjusted to other prognostic factors. **Results.** The results showed optimal cutoff values for PNI and LMR were 50.5 and 4.45, respectively. A high PNI (≧50.5) was significantly improved 5-year OS. A lower LMR (< 4.45) significantly associated with poor 5-year DFS, DSS and OS. In multivariate analysis, both PNI and LMR were independent prognosticators for 5-year OS. **Conclusions.** Elevated pretreatment PNI and LMR are both favorable prognosticators in advanced p16-negative oropharyngeal cancer patients undergoing CCRT.

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Abstract

Background.

Systemic inflammation and nutrition status both play roles in the survival of cancer patients. It would be valuable to study the effect of prognostic nutritional index (PNI) and lymphocyte-to-monocyte ratio (LMR) on survival in patients with advanced p16-negative oropharyngeal cancer.

Methods.

There were 142 patients who diagnosed advanced p16-negative oropharyngeal cancer between 2008 and 2015 enrolled in this study. All patients received primary treatment with definite concurrent chemoradiotherapy (CCRT). Optimal cutoff values of PNI and LMR were determined by receiver operating characteristic curve for survival prediction. Five-year overall survival (OS), disease-specific survival (DSS), and disease-free survival (DFS) rates for prognostic factors were also estimated. Effects of PNI and LMR on survival were assessed by Cox regression model with adjusted to other prognostic factors.

Results.

The results showed optimal cutoff values for PNI and LMR were 50.5 and 4.45, respectively. A high PNI ($\geqq$50.5) was significantly improved 5-year OS. A lower LMR ($<$ 4.45) significantly associated with poor 5-year DFS, DSS and OS. In multivariate analysis, both PNI and LMR were independent prognosticators for 5-year OS.

45 **Conclusions.**

46 Elevated pretreatment PNI and LMR are both favorable prognosticators in advanced p16-

47 negative oropharyngeal cancer patients undergoing CCRT.

Introduction

It is estimated that head and neck cancers are the sixth most diagnosed systemic malignant tumors, and there are more than 500,000 new cases and 300,000 associated deaths annually.(McGuire, 2016) Oropharyngeal squamous cell carcinoma (OPSCC) is an aggressive type of head and neck cancer. The average annual percentage increase of OPSCC is 6.1% between 1980 and 2014, the prevalence trend still increased and advanced stage disease while diagnosis in large portion of OPSCC patients were noted in Taiwan. (Hsu et al., 2017) Though investigations of OPSCC have been carried out for decades worldwide, its etiologic and clinical characteristics differ substantially among populations, such as human papillomavirus (HPV) infection on patients may lead to favorable prognosis result than those without HPV infection, therefore this disease still lack of consensus regarding the optimal treatment paradigm. (Mehanna et al., 2013) Besides, the relatively lower HPV infection rate, about 20-30%, in Taiwan along with the high prevalence of betel nut chewing habit had been investigated in our previous study,(Al-Swiahb et al., 2010) both make the evaluation of treatments and possible prognostic factor in advanced stage HPV-negative OPSCC an urgent need.

Other than HPV status inflammatory biomarkers are thought to be a representation of the interaction between the tumor microenvironment and host immune system.(O'Callaghan et al., 2010; Aggarwal, Vijayalekshmi & Sung, 2009) Recent studies showed a negative prognostic

value of higher neutrophil-to-lymphocyte ratio (NLR) and lower lymphocyte-to-monocyte ratio (LMR) among patients with head and neck cancer.(Perisanidis et al., 2013; Haddad et al., 2015; Rassouli et al., 2015; Tham et al., 2018) Takahashi et al.(Takahashi et al., 2019) reported that low LMR was an independent prognostic factor for survival in patients with OPSCC.

In addition to HPV and inflammatory biomarkers, nutritional impairment has also been shown to have a negative impact on clinical outcomes.(Moon et al., 2016) Patients with advanced stage OPSCC are usually vulnerable to malnutrition at the time of diagnosis because of poor food intake due to cancer-related pain, mechanical obstruction by tumor, or psychological problems. The prognostic nutritional index (PNI), calculated as previously described,(Onodera, Goseki & Kosaki, 1984) may be especially useful because it could act as a surrogate marker for both inflammation and nutritional status. This index was originally studied to demonstrate the correlation between postoperative complications and prognosis for patients affected by esophageal carcinoma.(Nozoe et al., 2002) With regard to head and neck cancer study, a low PNI has been shown to be a predictor of poor survival.(Bruixola et al., 2018)

Currently, studies on the role of PNI and LMR in patients with advanced stage HPV-negative OPSCC are still limited. Clinically, p16 expression could be regarded as a surrogate marker for HPV in the prediction of tumor behavior in oropharyngeal cancer. This study is aimed at identifying the clinical significance of PNI, LMR, and other clinicopathological variables in

84 patients with advanced stage (stage III/ IV) p16-negative OPSCC.

Material and Methods

Study population.

Patients who were histologically confirmed by biopsy to have stage III/IV p16-negative OPSCC were evaluated in the study. TNM stage was reclassified according to the 8th edition of the American Joint Committee on Cancer (AJCC) staging system. Patients who were treated with primary concurrent chemoradiotherapy (CCRT) were eligible for this study. The determination of p16 expression in tumor cells by immunohistochemistry was done as suggested in the 8th edition AJCC staging system manual.(Amin et al., 2017) Patients with clinical evidence of acute infection or who were diagnosed with recurrent tumors, distant metastases, other concomitant active cancers, or chronic inflammatory disease or history of malignancy in the past 5 years were excluded from the study.

In this retrospective study conducted between January 2008 and April 2015, 142 patients with stage III/IV p16-negative OPSCC underwent primary CCRT in Kaohsiung Chang Gung Memorial Hospital in Taiwan. Treatment was primarily based on the American NCCN guidelines. All patients received cisplatin-based chemotherapy and intensity-modulated radiotherapy on 5 consecutive days each week, at a conventional fractionated daily dose of 1.8 or 2 Gy. The total dose for radiotherapy was 70–74 Gy. The initial treatment volume included the tumor bed and regional lymphatics. After receiving 46–50 Gy, the treatment area was reduced to

irradiate the tumor bed and regional lymph nodes. All included patients completed the treatment programs formulated by the multidisciplinary team.

Variables and outcomes.

Pretreatment clinical variables of interest were collected, including age, sex, performance status (Eastern Cooperative Oncology Group, or ECOG, score), and staging of tumor. Pretreatment complete blood count (including absolute lymphocyte and monocyte counts) and biochemistry (including albumin) in peripheral blood test were also measured within one week before treatment.

The LMR was calculated by dividing the baseline absolute peripheral lymphocyte count (cells/mm^3) by the absolute monocyte peripheral count (cells/mm^3).

The PNI was calculated as follows: 10 × baseline serum albumin (g/dL) + 0.005 × baseline absolute lymphocyte count (cells/mm^3).

Statistical analysis.

Receiver operating curves for survival were plotted, and Youden's index was applied to verify the optimum cutoff value of LMR and PNI for overall survival. Survival rates of certain prognostic factors were estimated using Kaplan–Meier method, and the log-rank test was used to determine the heterogeneity of each specific factor. The variables, sex, and smoking status were excluded from analysis because of the extremely imbalanced distribution. Cox proportional

hazards model was built with independent primary factors and other significant prognostic factors that were identified in prior univariate survival analyses. The variance inflation factors (VIF) were assessed to avoid multicollinearity among independent variables in a Cox model. All tests were two-sided, and statistical significance was set at 0.05. All statistical analyses were carried out using the Statistical Package for the Social Sciences software, version 20.0 (SPSS, Chicago, IL). This study was approved by the Medical Ethics and Human Clinical Trial Committees at Chang Gung Memorial Hospital (Ethical Application Reference number:202000471B0). Patients' consent to review their medical records was not required by this hospital's committees because the patient data remained anonymous in this study.

Results

Of the 142 p16-negative OPSCC patients, 99.3% (141) were male and 0.7% (1) were female; the mean age of diagnosis for all was 53.8 years, ranging from 36 to 85 years. The ECOG performance status scores of patients in our cohort were all 0 and 1. The mean follow-up was 40.7 months (from 3.6 to 111.8 months). Nine patients (6.3%) had stage III disease, 34 patients (23.9%) had stage IVA disease, and 99 patients (69.7%) had stage IVB disease. For clinical T classification, this cohort included T1 (n = 4, 2.8%), T2 (n = 24, 16.9%), T3 (n = 24, 16.9%), T4a (n = 34, 23.9%), and T4b (n = 56, 39.4%). Clinical nodal metastasis was present in 117 patients (82.4%) and 65 patients (45.8 %) had extranodal extension (ENE). At the end of the study, 95 (66.9%) patients died; of these, 68 (47.9%) died of oropharyngeal cancer. The clinicopathological features of the 142 cases, and their survival outcomes were listed in Table 1.

The optimal cutoff value for PNI was 50.5, while that for LMR was 4.45 (Figure 1). For the possible correlation between PNI and LMR, the VIF was also assessed to detect collinearity. Both VIF values for continuous PNI to continuous LMR or dichotomous PNI to dichotomous LMR were below 3 (1.004 and 1.002). The result indicated that there was a low correlation between PNI and LMR.

The overall survival rate for patients with PNI$\geqq$50.5 was significantly increased, compared with patients with PNI<50.5 (48.1% vs 24.7%, p = 0.004). Similarly, the DSS for patients with

PNI≧50.5 was significantly increased, compared with patients with PNI<50.5 (57.2% vs 42%, p = 0.043). Moreover, DFS had a similar trend by PNI difference in our cohort (44.3% vs 34.2%), although p value did not reach statistical significance (p = 0.108, Figure 2). Regarding the LMR, the 5-year OS (55.5% vs 26.6%), DSS (66.8% vs 41.4%) and DFS (51.4% vs 35.0%) were all significantly increased (both $p < 0.05$, Figure 3) among patients with LMR≧4.45, compared with those with LMR < 4.45. Clinically positive ENE status was another significant predictor of poor outcome for 5-year OS, DSS, and DFS in univariate analysis (Table 2).

In multivariate analysis, PNI was an independent factor of OS in this cohort (hazard ratio [HR]: 1.778, 95% CI: 1.145–2.761) and simultaneously adjusted by other independent factors, LMR and ENE (Table 3). In another model, the status of LMR showed a significant prognosticator in OS (HR of 2.408, 95% CI: 1.439–4.029), DSS (HR: 2.33, 95% CI: 1.255–4.323), and DFS (HR: 1.765, 95% CI: 1.067–2.892) after being adjusted by other factors (Tables 3-5). The status of clinical ENE was a significant prognosticator of OS (HR: 1.592, 95% CI: 1.054–2.405), DSS (HR: 2.159, 95% CI: 1.319–3.533) and DFS (HR: 1.86, 95% CI: 1.202–2.878), respectively. (Table 3–5)

Discussion

In the current study of patients with advanced stage (stage III/IV) p16-negative OPSCC, its 5-year DFS, DSS, and OS rates were 39.9%, 49.8%, and 35.6%, respectively. In our study, PNI, LMR and clinical ENE status were all independent significant factors of overall survival in multivariate cox regression analysis. A low PNI implies a decrease in serum albumin and/or a lower absolute lymphocyte count. Serum albumin is an important factor of the host inflammatory response and nutritional status.(Gupta & Lis, 2010) The absolute lymphocyte count is also believed to be an important participant in the inhibition of cancer growth by initiating a cytotoxic immune response.(Mantovani et al., 2008) Taken together, this existing evidence showed that malnutrition and lymphocytopenia may be revealed as factors affecting a chronically impaired immune system. The cutoff value for PNI reported in previous studies in other solid cancer ranged between 40 and 60.(Feng & Chen, 2014; Lee et al., 2017; Jian-Hui et al., 2016; Shibutani et al., 2015; Yang et al., 2016) With regard to head and neck cancer, several studies found that lower PNI predicted poor oncologic outcome in HNSCC (Table 6).(Bruixola et al., 2018; Kono et al., 2017; Chang et al., 2018; Fu et al., 2016) Bruixola et al. demonstrated low PNI (cutoff value: 45) was an independent prognostic biomarker in locoregional advanced head and neck squamous cell carcinoma.(Bruixola et al., 2018) Fu et al. studied 975 patients with laryngeal squamous cell carcinoma treated by curative laryngectomy, and this study also demonstrated

patients with PNI < 48.65 had a low probability of cancer-specific survival and OS.(Fu et al., 2016) Our result is comparable with these findings, showing that a low PNI is a poor prognostic factor in patients with advanced stage (stage III/IV) p16-negative OPSCC undergoing primary CCRT, with a cutoff value similar to previous studies. In our study, patients with PNI < 50.5 have significantly reduced survival with adjusted by other prognostic factor in multivariate analysis.

In recent years, studies investigating the clinical effect of LMR on prognosis of head and neck squamous cell carcinoma (HNSCC) have increased. It is believed that the white blood cell differential in HNSCC tends toward either a myeloid or a lymphoid lineage. The lymphoid preponderance was associated with better disease outcomes based on previous studies. Several studies found that lower LMR predicted reduced disease-specific survival and OS in HNSCC (Table 7).(Takahashi et al., 2019; Tham et al., 2019; Furukawa et al., 2019; Yang et al., 2018; Kano et al., 2017) In addition, the relationship between LMR and advanced stage OPSCC was not thoroughly evaluated. Our result is comparable with these findings, showing that a low LMR is a poor prognostic factor in advanced stage (stage III/IV) p16-negative OPSCC with LMR < 4.45, having a significantly reduced OS, DSS and DFS that still remained significant on multivariate analysis.

The mechanism by which increased systemic inflammatory response and a low nutritional status promote tumor cell invasion, proliferation, and metastasis is not well understood. The following are possible explanations for the correlation between low PNI, low LMR, and poor prognosis in HNSCC patients. A low level of LMR implies a relative decrease in lymphocytes and monocytes. Lymphocytes play a crucial antitumoral role by inducing cytotoxic cell death, inhibiting tumor cell proliferation and migration, and instituting the host's immune response to cancer.(De Giorgi et al., 2012) Lesser amounts of infiltrating lymphocytes have been shown to correlate to poor prognosis.(Gooden et al., 2011) In contrast, increased levels of monocyte-derived macrophages have been shown to be associated with increased tumor aggressiveness and poorer survival outcomes.(Pollard et al., 2004) This is postulated to happen through tumor microenvironment mediators such as TNF-α, vascular endothelial growth factor, and epidermal growth factor.(Pollard et al., 2004; Xiong et al., 1998) Perhaps the prognostic ability of LMR is because it acts as a crude marker for the pro-tumor versus anti-tumor dynamic in the immune system.(Lin, Chien & Chuang, 2017)

PNI is composed of both serum albumin concentration and lymphocyte count and is used to assess immune-nutritional status and may predict the prognosis of cancer patients.(Yao et al., 2013) Several studies have shown that malnutrition, reflected by hypoalbuminemia and low lymphocyte counts, is associated with an immunosuppressed condition, which provides a

219 favorable microenvironment for tumor recurrence.(Colotta et al., 2009) This immunosuppressed
220 condition in low-PNI patients may cause the poor outcomes.

221 Several limitations that should be addressed in the current study. Firstly, this is a
222 retrospective, single-institute study, and there would be a selection bias during patient and data
223 collection. Secondly, the assessment of some reported inflammatory indicators, including
224 C-reactive protein, interleukin, and tumor necrosis factor, were not included in this study.

Conclusion

In summary, our current study showed that the pretreatment PNI and LMR based on standard laboratory measurements may be simple, noninvasive, inexpensive, and potentially effective indicators to evaluate the prognosis of advanced stage p16-negative OPSCC patients who underwent CCRT.

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Table 1(on next page)

Clinical characteristics of 142 patients who were diagnosed with advanced p16-negative OPSCC.

Table 1. Clinical characteristics of 142 patients who were diagnosed with advanced p16-negative OPSCC.

Characteristics		Value	%
Mean Age(range), yr		53.8 (36, 85)	
Mean follow up time (range), months		40.7 (3.7, 111.8)	
Sex	male	141	99.3
	female	1	0.7
Clinical Stage	III	9	6.3
	IVA	34	23.9
	IVB	99	69.7
Clinical T classification	T1	4	2.8
	T2	24	16.9
	T3	24	16.9
	T4a	34	23.9
	T4b	56	39.4
Clinical N classification	N0	25	17.6
	N1	15	10.6
	N2b	17	12
	N2c	20	14.1
	N3b	65	45.8
Clinical ENE	negative	77	54.2
	positive	65	45.8
PNI	unknown	7	4.9
	<50.5	79	55.6
	≧50.5	56	39.4
LMR	< 4.45	99	69.7
	≧4.45	43	30.3
Recurrence	No	59	41.5
	Yes	83	58.5
Last status	NED	35	24.6
	Alive with disease	12	8.5
	DOD	68	47.9
	DWOD	27	19.0

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Abbreviations

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Abbreviations

Abbreviations: OPSCC, oropharyngeal squamous cell carcinoma; PNI, prognostic nutritional index = 10*serum albumin (g/dl) + 0.005 * total lymphocyte count (/mm^3); ENE, extranodal extension; LMR, lymphocyte to monocyte ratio; NED, no evidence of disease; DOD, died of disease; DWOD, die without disease;

Table 2(on next page)

Univariate Analysis of Factors Impacting Survival (n= 142)

Table 2. Univariate Analysis of Factors Impacting Survival (n= 142).

Variable		Number	Event	5yr OS (%)	*p*	Event	5 yr DSS (%)	*p*	Event	5 yr DFS (%)	*p*
Age	<53	70	45	38.1	0.489	34	49.5	0.836	44	35.3	0.743
	≧53	72	50	33.2		34	50.1		39	44.3	
Betel nut chewing	no	36	26	36.1	0.841	16	55.7	0.672	18	48.7	0.416
	yes	106	69	35.5		52	47.7		65	36.9	
Alcohol drinking	no	24	13	49.0	0.226	9	61.6	0.327	11	52.1	0.221
	yes	118	82	32.8		59	46.9		72	37.3	
Clinical T classification	T1/2/3	52	34	33.5	0.693	24	50.5	0.638	29	43.6	0.407
	T4a/b	90	61	36.7		44	49.4		54	37.7	
Clinical N classification	N0	25	18	35.6	0.684	11	50.7	0.801	15	36.3	0.884
	N1-N3b	117	77	35.5		57	49.6		68	40.6	
Clinical ENE	negative	77	48	41.0	0.037*	29	59.4	0.003*	38	49.7	0.008*
	positive	65	47	29.1		39	38.6		45	28.2	
PNI	<50.5	79	61	24.7	0.004*	43	42.0	0.043*	50	34.2	0.108
	≧50.5	56	31	48.1		23	57.2		31	44.3	
LMR	< 4.45	99	75	26.6	0.001*	54	41.4	0.01*	62	35.0	0.042*
	≧4.45	43	20	55.5		14	66.8		21	51.4	

Abbreviations: *, statistically significant ($p<0.05$); OS, overall survival; DSS, disease specific survival; DFS, disease free survival; ENE, extranodal extension; PNI, prognostic nutritional index; LMR, lymphocyte to monocyte ratio.

Table 3(on next page)

Multivariate analysis of prognostic factors associated to overall survival.

1 Table 3. Multivariate analysis of prognostic factors associated to overall survival.

Factor	Hazard ratio	95% CI	*p*-value
PNI			0.01*
≧50.5	1		
< 50.5	1.778	(1.145, 2.761)	
LMR			0.001*
≧4.45	1		
< 4.45	2.408	(1.439, 4.029)	
ENE			0.027*
negative	1		
positive	1.592	(1.054, 2.405)	

2 Abbreviations: *, statistically significant (p<0.05); ENE, extranodal
3 extension; PNI, prognostic nutritional index; LMR, lymphocyte to
4 monocyte ratio.

Table 4(on next page)

Multivariate analysis of prognostic factors associated to disease-specific survival.

Table 4. Multivariate analysis of prognostic factors associated to disease-specific survival.

Factor	Hazard ratio	95% CI	*p*-value
PNI			0.066
≧50.5	1		
< 50.5	1.624	(0.968, 2.723)	
LMR			0.007*
≧4.45	1		
< 4.45	2.33	(1.255, 4.323)	
ENE			0.002*
negative			
positive	2.159	(1.319, 3.533)	

Abbreviations: *, statistically significant (p<0.05); ENE, extranodal extension; PNI, prognostic nutritional index; LMR, lymphocyte to monocyte ratio.

Table 5(on next page)

Multivariate analysis of prognostic factors associated to disease-free survival.

1 Table 5. Multivariate analysis of prognostic factors associated to disease-free survival.

Factor	Hazard ratio	95% CI	*p*-value
LMR			0.027*
≧4.45	1		
< 4.45	1.765	(1.067, 2.892)	
ENE			0.005*
Negative	1		
Positive	1.86	(1.202, 2.878)	

2 Abbreviations: *, statistically significant (p<0.05); ENE, extranodal extension;

3 LMR, lymphocyte to monocyte ratio.

Table 6(on next page)

Different studies about PNI in HNSCC.

Table 6. Different studies about PNI in HNSCC.

Reference	Site	Case number	Cut off for PNI	Primary treatment strategy	Statically significant Outcome measurement
Bruixola G et al.[20]	Locoregionally advanced HNSCC	145	45	ICT followed by CCRT	OS
Kono et al.[27]	HNSCC	101	40	Radiotherapy	toxicity of radiotherapy
Chang et al.[28]	Advanced oral cavity, oropharynx, hypopharyngeal cancer	143	36	CCRT	treatment tolerance and toxicity of CCRT
Fu et al.[29]	Laryngeal squamous cell carcinoma	975	48.65	Radical surgery	DSS and OS
Our current study	Advanced stage p16 negative OPSCC	142	50.5	CCRT	OS

Abbreviations: PNI, prognostic nutritional index; HNSCC, head and neck squamous cell carcinoma; OPSCC, oropharyngeal squamous cell carcinoma; ICT, induction chemotherapy; CCRT, concurrent chemoradiotherapy; OS, overall survival; DSS, disease-specific survival.

Table 7 (on next page)

Different studies about LMR in HNSCC.

Table 7. Different studies about LMR in HNSCC.

Reference	Site	Case number	Cutoff for LMR	Primary treatment strategy	Statically significant Outcome measurement
Takahashi et al.[12]	Oropharyngeal carcinoma	75	4.97	Heterogeneity (76% of population were CRT)	OS
Tham et al.[30]	HNSCC	123	2.8	Radical surgery	Event free survival
Furukawa et al.[31]	Tongue cancer	103	4.29	Radical surgery	OS
Yang et al.[32]	Hypopharyngeal carcinoma	197	2.98	Not well documented	OS, DSS and DFS
Kano et al.[33]	Oropharyngeal, hypopharyngeal, and laryngeal cancers	285	3.22	Concurrent CRT	OS and DFS
Our current study	Advanced stage p16 negative OPSCC	142	4.45	Concurrent CRT	OS, DSS and DFS

Abbreviations: LMR, lymphocyte to monocyte ratio; HNSCC, head and neck squamous cell carcinoma; OPSCC, oropharyngeal squamous cell carcinoma; CRT, chemoradiotherapy; OS, overall survival; DSS, disease-specific survival; DFS, disease-free survival.

Figure 1

Receiver operating characteristic curve of (A) PNI and (B) LMR for predicting the survival outcome among patients with advanced p16-negative OPSCC

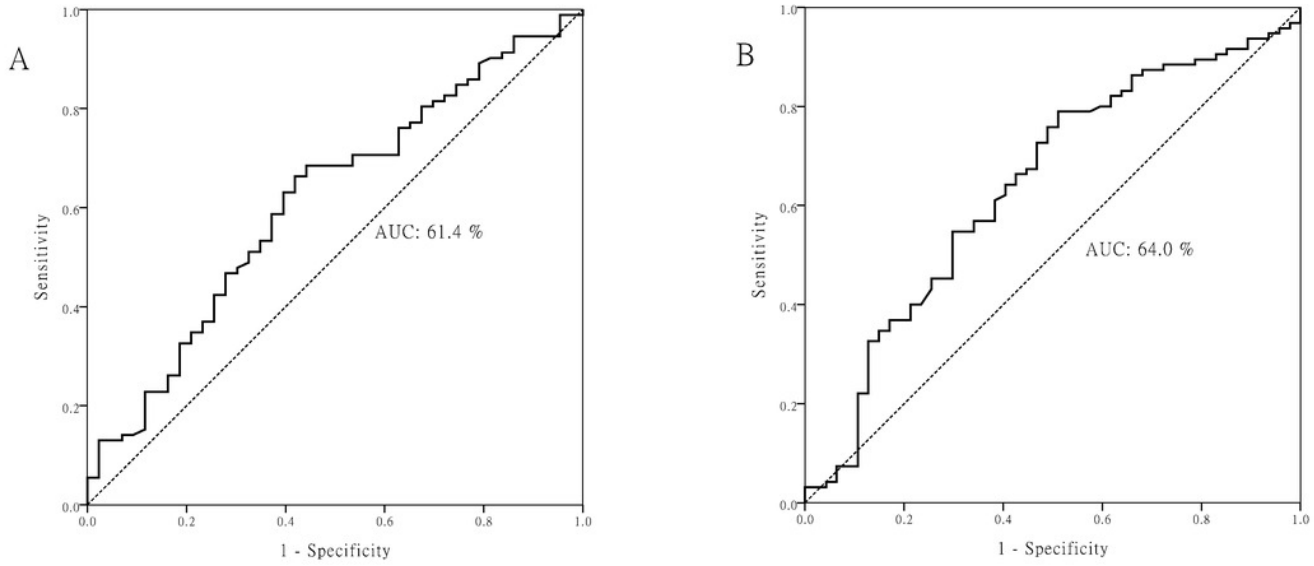

Figure 2

Kaplan-Meier survival curves for patients with advanced p16-negative OPSCC, comparing patients in PNI < 50.5 to PNI >= 50.5.

(A) Overall survival, (B) disease-specific survival, and (C) disease-free survival.

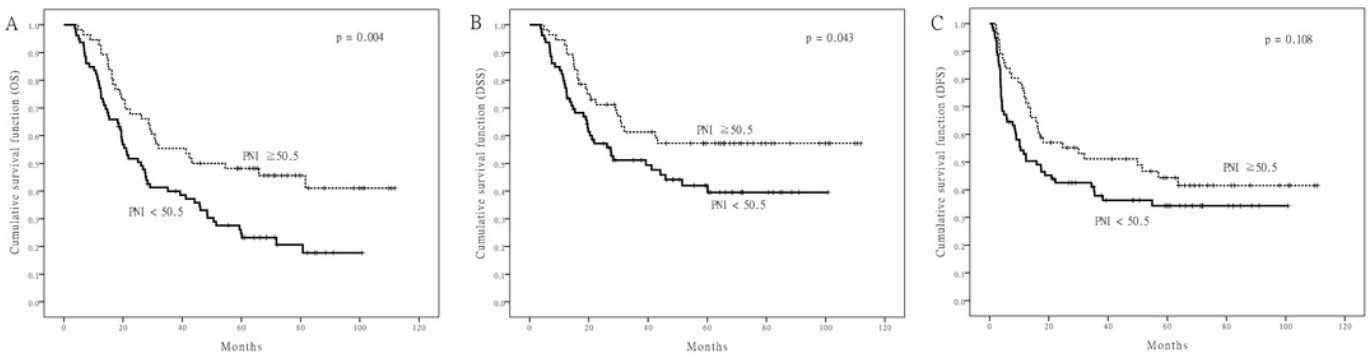

Figure 3

Kaplan-Meier survival curves for patients with advanced p16-negative OPSCC by different LMR levels with threshold 4.45.

(A) Overall survival, (B) disease-specific survival, and (C) disease-free survival.