Risk Classification of Human Papillomavirus-related Oropharyngeal Squamous Cell Carcinoma in Japanese Patients

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Abstract

Purpose The validity of the risk classification according to Ang for human papillomavirus (HPV)-related oropharyngeal squamous cell carcinoma (OPSCC) remains to be studied in patients treated by methods other than chemoradiotherapy and in Japanese patients. In this study, the validity of Ang's risk classification was studied in Japanese patients treated using various methods, including surgery.

Material and Method Between 2010 and 2018, 122 patients with HPV-related OPSCC stages III and IV according to the TNM classification 7th edition (TNM-7) were treated curatively at a single institution in Japan. The median age was 62.7 years. Sixty-seven patients (54.9%) were classified as stage I according to the TNM 8th edition (TNM-8). Over 50% of the patients underwent surgery with or without adjuvant therapy. The influence of multiple factors on survival was determined.

Results Age, amount of smoking, secondary cancer, and N-stage according to the TNM-7 significantly influenced survival. Ang's risk classification was also predictive of prognosis, but if 30 pack-years (PYs) instead of 10 PYs is employed to dichotomize the amount of smoking, the new risk classification can significantly better predict prognosis. According to the new risk classification, favorable and unfavorable risk patients showed 5-year progression-free survival, disease-specific survival, and overall survival rates of 72.7% and 35.9%, 94.6% and 76.2%, and 92.6% and 62.7%, respectively.

Conclusions Even in patients treated by methods other than chemoradiotherapy and in Japanese patients, the combination of the amount of smoking and neck node status is useful in prognosis prediction.

Background

The incidence of human papillomavirus (HPV)-related oropharyngeal squamous cell carcinoma (OPSCC) is increasing rapidly in developed countries [1]. In Japan, a similar increase in HPV-related OPSCC has been observed [2]. In contrast to HPV-unrelated OPSCC, HPV-related OPSCC has been reported to have a favorable prognosis [3–6]. Although tobacco smoking is one of the major causes and prognostic factors of HPV-unrelated OPSCC, the prognostic impact of tobacco smoking remains controversial in HPV-related OPSCC [7–10]. A milestone study by Ang et al. revealed the impact of tobacco smoking on overall survival (OS) and progression-free survival (PFS) in HPV-related OPSCC, and the amount of smoking expressed by pack-years (PYs) ≤10 or PY >10 was used as one of the criteria for risk classification along with the extent of neck lymph node involvement [3]. The risk classification according to Ang was derived from HPV-related OPSCC patients treated exclusively with chemoradiation therapy according to the RTOG 0129 protocol [3]. However, it has not yet been reported whether the risk classification is also valid in HPV-related OPSCC patients treated with other modalities such as surgery, and a validity analysis has not been performed in Japanese patients with HPV-related OPSCC.

In this retrospective study, the validity of Ang's risk classification was verified in patients with HPV-related OPSCC treated with various modalities in a single institution in Japan. Additionally, we studied whether a

modification of Ang's risk classification can improve the predictive power with respect to prognosis.

Materials And Methods

Patients

This single center retrospective study was approved by the Institutional Review Board (No. 2017-091 and 2018-179). Because of the retrospective nature of this study, informed consent was waived.

Between 2010 and 2018, 240 patients with non-metastatic OPSCC with a known p16 status were treated at a single institution in Japan; of these, 143 (59.6%) had p16-positive OPSCC and 97 (40.4%) had p16-negative OPSCC. To diagnose HPV-related OPSCC, p16 immunohistochemical staining (IHC) was used as a surrogate in this study. An expert head and neck pathologist (YM) diagnosed p16 positivity if nuclear and cytoplasmic staining was apparent in >75% of tumor cells. Two of the 143 patients with HPV-related OPSCC were treated palliatively because of poor performance status and were excluded from this study, and the remaining 141 patients were treated with curative intent. Because the study by Ang et al. analyzed only OPSCC patients in stages more advanced than T1-2N0M0 in the TNM 7th edition (TNM-7) [3], 19 patients with T1-T2N0M0 (TNM-7) were excluded from further analysis. The remaining 122 patients with p16-positive OPSCC in stages III and IV in TNM-7 were analyzed in this study. The clinical characteristics of these 122 patients are presented in Table 1. More than 80% of patients were men and the median age was 62.7 years (range, 35–83 years). Approximately 72% of all patients were current or former smokers. The amount of tobacco smoking is expressed in PYs with a median of 25.3 PY among smokers. Synchronous or metachronous secondary cancers were found in 35 patients (28.7%). Alcohol intake was not considered in this study because of the lack of detailed information on the type of alcohol consumed.

Table 1
Patient characteristics and univariate analysis of prognosis according to the possible prognostic factors.

		n (%)		5-year PFS	p	5-year DSS	p	5-year OS	p
Gender									
	male	99	(81.1%)	64.5%	0.78	89.4%	0.92	84.3%	0.91
	female	23	(18.9%)	67.8%		95.5%		91.3%	
Age									
	median	62.7 years							
	< 70 years	92	(75.4%)	70.4%	0.12	96.6%	0.008	91.9%	0.006
	≥ 70 years	30	(24.6%)	51.6%		72.8%		67.7%	
Smoking habit									
	never	34	(27.9%)	63.2%	0.68	88.2%	0.85	85.6%	0.78
	ever	88	(72.1%)	66.0%		91.5%		85.6%	
	median PY for ever smokers	25.3 PY							
	≤ 10 PY	48	(39.3%)	72.3%	0.37	92.1%	0.52	90.2%	0.42
	> 10 PY	74	(60.7%)	60.6%		89.9%		83.1%	
	≤ 30 PY	84	(68.9%)	70.5%	0.23	93.9%	0.04	91.6%	0.012
	> 30 PY	38	(31.1%)	52.2%		82.4%		72.4%	
Secondary cancer									
	yes	35	(28.7%)	62.2%	0.82	87.2%	0.13	74.0%	0.006
	no	87	(71.3%)	67.2%		92.0%		90.9%	
Primary site									
	tonsil	91	(74.6%)	62.4%	0.81	90.9%	0.25	84.3%	0.381
	base of tongue	28	(23.0%)	74.2%		92.6%		92.6%	
	others	3	(2.5%)	66.7%		66.7%		66.7%	
T stage (8th Ed.)									

CRT: concurrent chemoradiotherapy, DSS: disease-specific survival, NeoCT: neoadjuvant chemotherapy, OP: operation, OS: overall survival, PFS: progression-free survival, RT: radiation therapy, PY: pack-year.

	n (%)		5-year PFS	p	5-year DSS	p	5-year OS	p
T1	17	(13.9%)	82.4%	0.68	94.1%	0.44	94.1%	0.76
T2	61	(50.0%)	64.5%		91.0%		84.5%	
T3	16	(13.1%)	52.4%		87.5%		87.5%	
T4	28	(23.0%)	66.8%		92.0%		84.7%	
N stage (8th Ed.)								
N0	5	(4.1%)	60.0%	0.077	100.0%	0.44	100.0%	0.68
N1	95	(77.9%)	67.3%		90.4%		85.2%	
N2	18	(14.8%)	64.6%		93.3%		86.2%	
N3	4	(3.3%)	25.0%		75.0%		75.0%	
N stage (7th Ed.)								
N0-N2a	33	(27.0%)	81.30%	0.072	100.0%	0.051	100.0%	0.01
N2b-N3	89	(73.0%)	59.50%		87.2%		80.5%	
N0-N2b	100	(82.0%)	66.90%	0.52	91.5%	0.075	86.4%	0.24
N2c-N3	22	(18.0%)	57.60%		85.9%		81.3%	
Clinical stage (8th Ed.)								
I	67	(54.9%)	67.3%	0.88	91.8%	0.46	85.9%	0.74
II	25	(20.5%)	65.0%		91.3%		91.3%	
III	30	(24.6%)	62.4%		89.3%		82.4%	
Treatment								
OP alone	27	(22.1%)	63.0%	0.78	91.6%	0.66	91.6%	0.42
OP + RT or OP + CRT	38	(31.2%)	61.3%		91.5%		56.3%	
RT alone	10	(8.2%)	60.0%		67.5%		67.5%	
CRT	36	(29.5%)	69.4%		94.3%		82.3%	
NeoCT + CRT	11	(9.0%)	72.7%		100.0%		100.0%	

CRT: concurrent chemoradiotherapy, DSS: disease-specific survival, NeoCT: neoadjuvant chemotherapy, OP: operation, OS: overall survival, PFS: progression-free survival, RT: radiation therapy, PY: pack-year.

	n (%)		5-year PFS	p	5-year DSS	p	5-year OS	p
Ang's risk classification								
low	70	(57.4%)	74.6%	0.021	94.3%	0.065	92.9%	0.016
intermdeiate	52	(42.6%)	52.0%		85.6%		76.2%	
New risk classification								
favorable	95	(77.9%)	72.7%	0.008	94.6%	0.002	92.6%	< 0.01
unfavorable	27	(22.1%)	35.9%		76.2%		62.7%	

CRT: concurrent chemoradiotherapy, DSS: disease-specific survival, NeoCT: neoadjuvant chemotherapy, OP: operation, OS: overall survival, PFS: progression-free survival, RT: radiation therapy, PY: pack-year.

Staging was performed with physical examinations, laryngopharyngeal endoscopy, computed tomography (CT), and magnetic resonance imaging (MRI). Positron emission tomography (PET)-CT or PET-MRI was performed in selected patients. More than 70% of the patients had a primary lesion in the tonsil, which was followed by base of the tongue primary in terms of frequency. Stage classification was performed according to the TNM 8th edition (TNM-8) and N classification (N-7) of the TNM-7. Sixty-seven patients were classified as stage I by the TNM-8.

Treatment

Regarding treatment, 65 (53.3%) patients underwent surgery with or without adjuvant radiation or chemoradiotherapy. Primary resection and neck dissection were performed in 62 patients, of whom seven with base of the tongue primary underwent bilateral neck dissection. In the remaining three patients, neck lymph node metastasis was managed by neck dissection, while the primary site was irradiated definitively. Thirty-eight of the 65 surgically treated patients were irradiated postoperatively, of which 15 patients underwent chemotherapy concurrently with postoperative radiotherapy.

The remaining 57 patients were managed with definitive radiation therapy with (47 patients) or without (10 patients) concurrent chemotherapy. Neoadjuvant chemotherapy was administered to 11 of the 47 patients treated with concurrent chemoradiotherapy. The neoadjuvant chemotherapy regimen was DCF (docetaxel 75 mg/m^2 on day 1, cis-platinum 75 mg/m^2 on day1, 5-FU 750 mg/m^2 from day 1 to day 5, repeated at 21-day intervals) in nine patients, and CF (cis-platinum 100 mg/m^2 on day 1 and 5-FU 1000 mg/m^2 from day 1 to 5, repeated at 21-day intervals) in two patients.

In total, 62 patients underwent concurrent chemotherapy with definitive or postoperative irradiation. In 47 patients, triweekly cis-platinum (80 mg/m^2) was administered, while cetuximab was administered to 15 patients with a priming dose of 400 mg/m^2 and an ensuing weekly dose of 250 mg/m^2 because of poor renal function.

Definitive and postoperative radiation therapies using 6 MV X-rays from accelerators (Varian, Palo Alto, CA, USA) were performed with intensity-modulated radiation therapy in 93 out of 95 patients. In the definitive radiation, the gross tumor volume was irradiated with doses between 60 and 70 Gy in conventional fractionation. Prophylactic neck regions were irradiated up to 54 Gy. Postoperative irradiation to the bilateral necks was delivered in doses between 50 and 60 Gy in a conventional fractionation in cases with positive operative margins, multiple lymph node involvement, and/or extranodal invasion, with a boost dose of 6-10 Gy at the sites of extranodal invasion or positive margins. Doses of <60 Gy were applied in only two patients who were irradiated postoperatively.

Statistical analysis

Progression-free survival (PFS), disease-specific survival (DSS), and overall survival (OS) were calculated using the Kaplan-Meier method, assuming the date of treatment initiation as day 0. For the calculation of PFS, recurrence and death from any cause were considered as events. For the calculation of DSS, death by tumor was considered as an event, and patients who died without developing recurrence and patients who were alive at the final follow-up were censored. The difference between survival curves was tested using the log-rank test. Multivariate analysis (MVA) using Cox proportional hazard regression models was performed with PFS, DSS, and OS as endpoints. Variables with p-values of <0.1 in the univariate analyses (UVA) were included in the MVA. All analyses were performed using SPSS ver. 26. The median follow-up period for all patients was 52 months.

Results

For all 122 patients, the PFS, DSS, and OS were 75.4%, 96.7%, and 95.1% at 3 years and 65.2%, 90.5%, and 85.6% at 5 years, respectively (Fig. 1). By applying the TNM-8, the 5-year PFS, DSS, and OS were 67.3%, 91.6%, and 85.6% for those with stage I, 65.0%, 91.7%, and 91.7% for those with stage II, and 62.4%, 89.3%, and 82.4% for those with stage III, respectively. The clinical stage according to the TNM-8, the primary site, and the treatment method did not significantly influence the PFS, DSS, and OS (Table 1).

In contrast, age group, amount of smoking, and presence of secondary cancers significantly affected survival. Patients aged ≥70 years of age showed unfavorable DSS (p = 0.008) and OS (p = 0.006) compared to younger patients. The amount of smoking was dichotomized at 10 PYs and 30 PYs and the dichotomizing point at which the PYs had a significant influence on survival was examined. Although a dichotomy at 10 PYs did not show any significant influence on survival, a dichotomy at 30 PY had a significant influence on DSS and OS. For patients who smoked ≤30 PYs and >30 PYs, the DSS was

93.9% and 82.4% (p = 0.04) at 5 years, and OS was 91.6% and 72.4% (p = 0.012) at 5 years, respectively. The presence of secondary cancers had a significant effect on OS (p = 0.006).

According to the risk classification of Ang [3], HPV-related OPSCC is classified into low and intermediate risk for death according to the number of PYs and N-7 stages. Patients with a smoking history of ≤10 PYs, and >10 PYs but with N0-N2a by N-7 were classified into the low-risk group. The remaining patients with HPV-related OPSCC without distant metastasis were classified into the intermediate-risk group. In the present study, 70 of the 122 patients were classified into the low-risk group and 52 into the intermediate-risk group according to Ang's risk classification. The low-and intermediate-risk groups significantly differed in PFS (p = 0.021) and OS (p = 0.016) and a near significant difference was observed in DSS (p=0.065). However, in the current study, the dichotomy of PYs at 10 did not have a significant influence on PFS, DSS, and OS, while PYs dichotomized at 30 had a significant influence on DSS and OS. Therefore, modified risk criteria were conceived wherein ≤30 and >30 PYs were used instead of ≤10 and >10 PYs. In contrast to the report by Ang et al., in which HPV-unrelated OPSCC was also included and a three-tiered risk classification was proposed, this study focused only on HPV-related OPSCC; therefore, the defined risk groups were named as favorable and unfavorable risk groups. The favorable risk and unfavorable risk groups according to the modified new risk classification significantly differed in PFS (p = 0.008), DSS (p = 0.002), and OS (p < 0.01). The PFS, DSS, and OS rates at 5 years were 72.7%, 94.6%, and 92.6% for the favorable risk group and 35.9%, 76.2%, and 62.7% for the unfavorable risk group, respectively (Fig. 2).

MVA was performed using the variables with a p-value of <0.1 in the UVA (Table 2). The MVA revealed that the new risk classification had a significant influence on PFS, DSS, and OS, while Ang's risk classification lost significance in the MVA.

Table 2
Results of multivariate analysis

	PFS		DSS		OS	
	p	HR	p	HR	p	HR
Age						
< 70 years vs. ≧ 70 years			0.029	0.24	0.012	0.29
Smoking						
≦ 30 PY vs. > 30 PY			0.41		0.28	
Secondary cancer					0.12	
N-8	0.089					
N0-N2a vs. N2b-N3	0.25		0.11		0.96	
N0-N2b vs. N2c-N3			0.091			
Ang’s risk classification	0.32		0.86		0.64	
New risk classification	0.01	2.29	0.011	5.15	0.027	3.012

DSS: disease-specific survival, HR: hazard ratio, N-8: nodal stage by TNM-8, OS: overall survival, PFS: progression-free survival, PY: pack-year.

Discussion

This study aimed to verify the validity of Ang's risk classification in patients with HPV-related OPSCC treated with various modalities in a single institution in Japan.

HPV-related OPSCC is known to have different etiologies and therapeutic responses to HPV-unrelated OPSCC. HPV-related OPSCC is caused by infection with high-risk HPV and responds well to therapeutic interventions with a favorable prognosis, in contrast to HPV-unrelated OPSCC [3–6]. The TNM-8 separates HPV-related and HPV-unrelated OPSCC, taking into account the etiological and prognostic differences. The TNM-8 uses p16 positivity as a surrogate marker for HPV infection, similar to the methods employed in this study. Although some studies have reported better differentiation of OS according to the stages of the TNM-8 than by the stages of the TNM-7 [11–14], some reports indicate that prognosis is inadequately differentiated by the TNM-8 [15, 16]. The current study also showed that the stages defined by the TNM-8 were inadequate in differentiating PFS, OS, and DSS. The OS of patients with stage III in this study was better than that of the other reported series [11–14]. DeFelice et al. also demonstrated a favorable 5-year OS of 86.2% in patients with stage III HPV-related OPSCC and denied the utility of the TNM-8 [15].

Because of the favorable prognosis of HPV-related OPSCC, therapeutic de-escalation has been attempted [17–19]. However, to demonstrate the validity of de-escalated therapeutic strategies, it is vital to select patients who can be managed with less intensive therapy [17, 19]. To identify appropriate patients, proper prognostic criteria are indispensable, and the TNM-8 staging seems to be inadequate to extract HPV-related OPSCC patients with a good prognosis who would be candidates for de-escalated treatment.

The risk classification proposed by Ang et al. was derived from patients treated exclusively with chemoradiation therapy [3]. Studies have demonstrated the validity of Ang's risk classification in HPV-related OPSCC patients managed by radiation therapy with and without chemotherapy [15, 20–23], but its validity has not been confirmed in surgically treated patients and Japanese patients. The current study demonstrated that Ang's risk classification is effective in differentiating the prognosis of HPV-related OPSCC in a Japanese population treated using various modalities including surgery. In this series, the amount of smoking dichotomized at 30 could better differentiate prognosis than when dichotomized at 10 PYs, as used in Ang's risk classification. It remains unclear whether this difference is due to the different sensitivities of the Japanese population to tobacco smoking, as ethnic differences in the effects of tobacco smoking on carcinogenesis have been reported [24, 25]. However, if we replace the division at 10 PYs with 30 PYs, the new classification can differentiate PFS, DSS, and OS quite well, with significant differences observed in both the UVA and MVA.

This study demonstrated that the basic principles of Ang's risk classification combining smoking PYs and N-7 stage are valid for identifying Japanese HPV-related OPSCC patients with a good prognosis who are treated by various strategies including surgery. In the TNM-8, bilateral involvement of neck lymph nodes (N2c in TNM-7) is classified as a higher N stage [11]. However, the current series showed that unilateral multiple lymph node involvement (N2b in TNM-7) is more predictive of an unfavorable prognosis of HPV-related OPSCC, which is similar to findings of Ang [3]. Using the new risk classification, a larger number of patients are classified into the favorable risk group than when using Ang's risk classification, which suggests that more patients would be candidates for the therapeutic de-escalation trial in HPV-related OPSCC.

The retrospective nature of this study limits its value. Additionally, important information regarding alcohol consumption, which was reported to be a significant prognosticator, is lacking in this study [26]. The proposed risk classification method must be validated in a prospective trial involving Japanese patients.

Conclusions

In the current series, the TNM-8 could not adequately differentiate the prognosis of patients with HPV-related OPSCC. In contrast, the combination of smoking PYs and N stage by TNM-7, such as in Ang's risk classification, could better differentiate prognosis and was shown to be valid even in Japanese patients treated with surgery as well as chemoradiotherapy. However, by replacing the cutoff point of 10 PYs in

Ang's risk classification with a cutoff point of 30 PYs, the prognosis of patients with HPV-related OPSCC could be better differentiated.

Abbreviations

CDDP: cis-diamine-dichloro-platinum, CRT: concurrent chemoradiotherapy, CT: computed tomography, DSS: disease-specific survival, HPV: human papillomavirus, HR: hazard ratio, IMRT: intensity modulated radiation therapy, MRI: magnetic resonance imaging, MVA: multivariate analysis, N-7: nodal stage by TNM 7th edition, N-8: nodal stage by TNM 8th edition, NeoCT: neoadjuvant chemotherapy, OP: operation, OPSCC: oropharyngeal squamous cell carcinoma, OS: overall survival, PET: positron emission tomography, PFS: progression-free survival, PY: pack-year, RT: radiation therapy, TNM: tumor, node, and metastasis, UVA: univariate analysis.

Declarations

Ethics approval and consent to participate

This single center retrospective study was approved by the Institutional Review Board (National Cancer Center No. 2017-091 and 2018-179). Because of the retrospective nature of this study, informed consent was waived.

Consent for publication

All the authors agreed to publish this manuscript in BMC cancer.

Availability of data and material

The datasets used and analysed during the current study are available from the corresponding author on reasonable request after the approval of National Cancer Center review board.

Competing Interests

J Itami reports grants and lecture honoraria from ITOCHU and Elekta, personal fees from Hekabio, AlphaTau, and Palette Life Science.

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Author's contributions

JI, KK, NM, GO, FM, and SY designed the study, TM did the p16 immunohistochemistry and diagnosis, YH reviewed chemotherapy, YK reviewed radiological examinations, KO, KI, KT, TK, YS, AT, YN collected clinical records, the results were interpreted by JI, KK, FM, SY, and HI. All the coauthors approved to submit this study to "BMC cancer".

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Figures

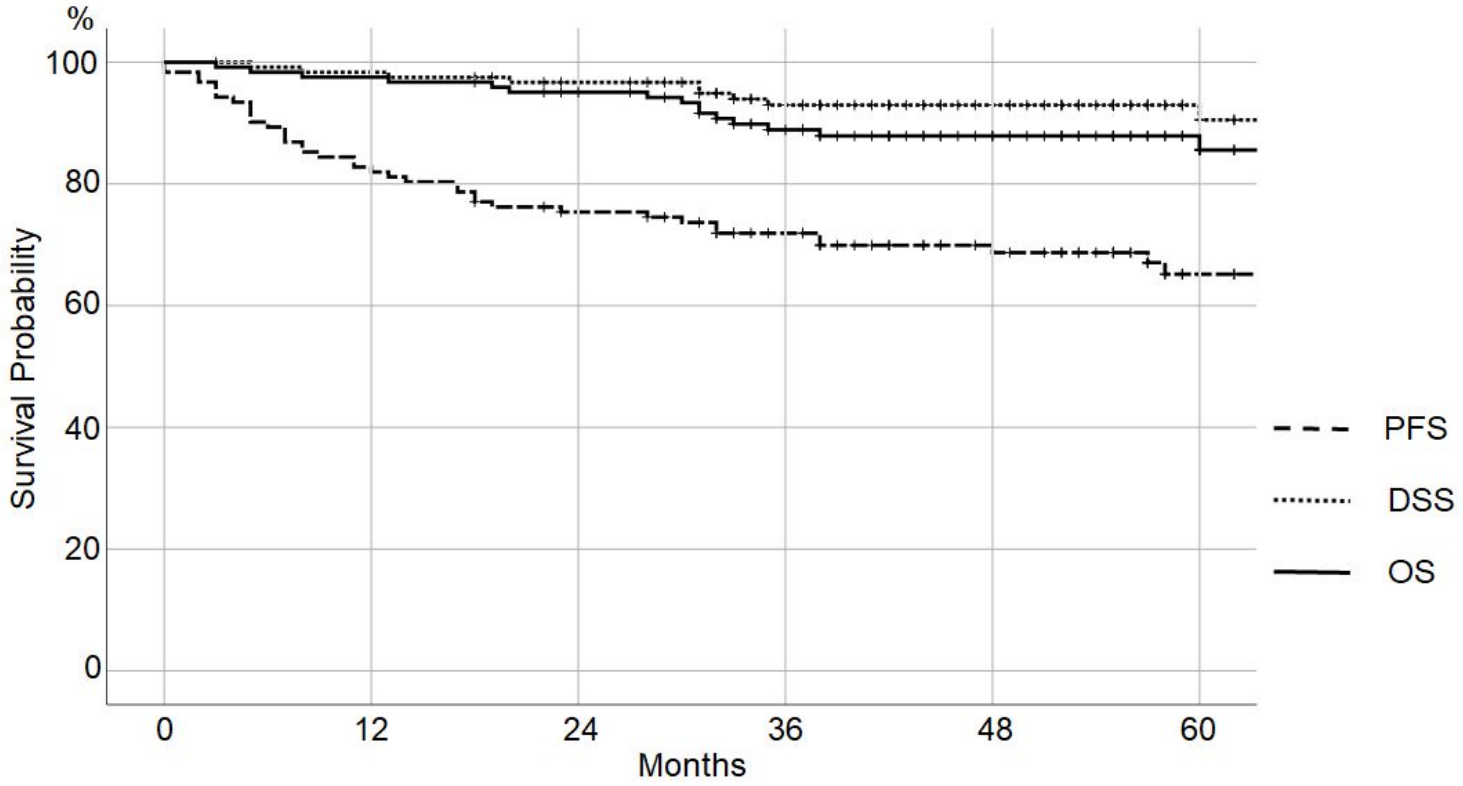

Figure 1

Kaplan-Meier curves. Progression-free survival (PFS), disease-specific survival (DSS), and overall survival (OS) of the 122 patients with human papillomavirus-related oropharyngeal squamous cell carcinoma in the clinical stages III and IV according to the TNM 7th edition who were treated between 2010 and 2018.

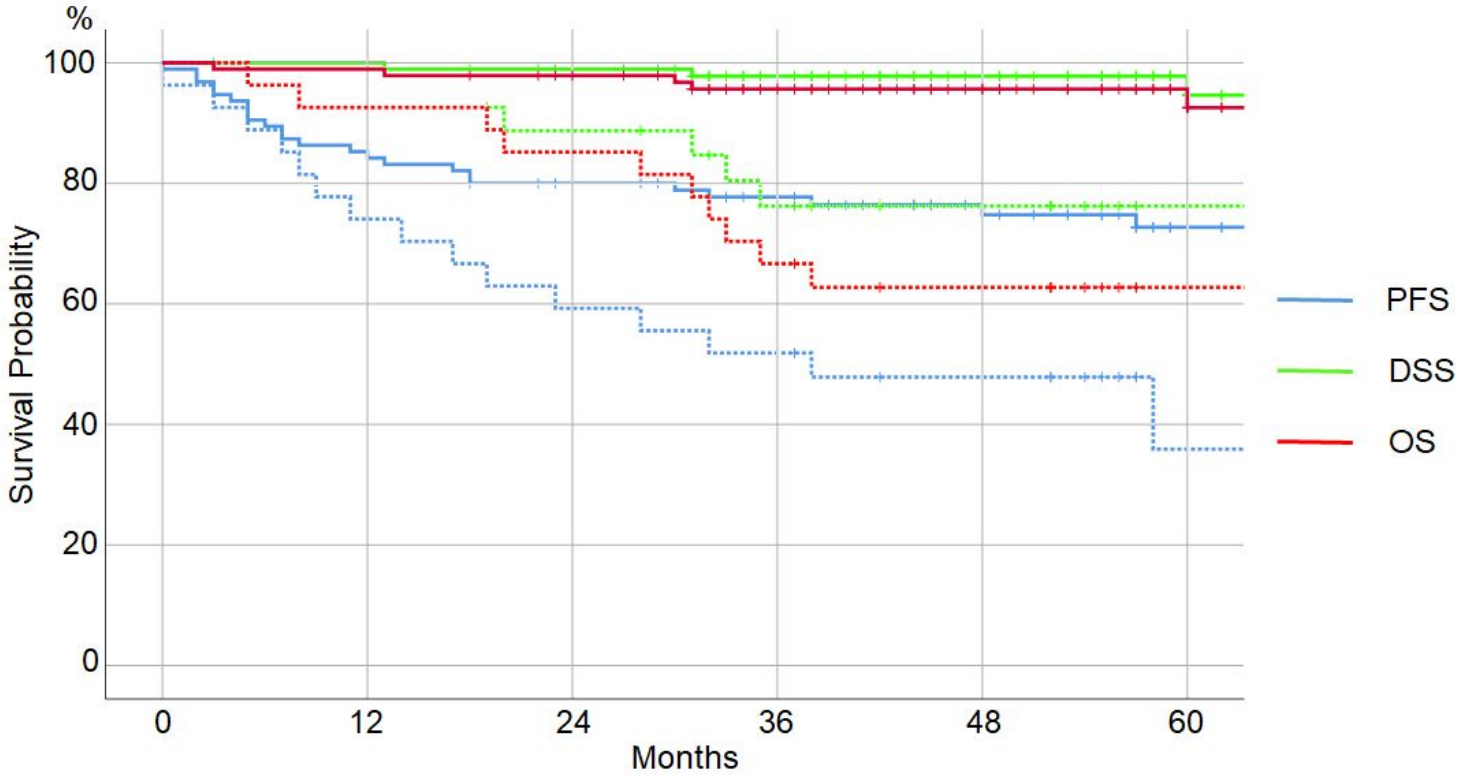

Figure 2

Kaplan-Meier curves. Progression-free survival (PFS) (blue), disease-specific survival (DSS) (green), and overall survival (OS) (red) according to the new risk classification. Solid line: favorable risk, broken line: unfavorable risk.