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Antibody Responses to Cancer Antigens Identify Patients with a Poor Prognosis among HPV-Positive and HPV-Negative Head and Neck Squamous Cell Carcinoma Patients

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Abstract

Purpose: The identification of high-risk patients within human papillomavirus (HPV)-positive and -negative head and neck squamous cell carcinoma (HNSCC) is needed for improved treatment and surveillance strategies. In this study, we set out to discover antibody responses (AR) with prognostic impact in HNSCC stratified by HPV status.

Experimental Design: A fluorescent bead–based multiplex serology assay on 29 cancer antigens (16 cancer-testis antigens, 5 cancer-retina antigens, and 8 oncogenes) and 29 HPV antigens was performed in samples of 362 patients with HNSCC from five independent cohorts (153 HPV positive, 209 HPV negative). A multivariable Cox proportional hazard model with bootstrapping ($M = 1000$) was used for validation of prognostic antibody responses.

Results: Antibody response to any of the cancer antigens was found in 257 of 362 patients (71%). In HPV-negative patients, antibody responses to c-myc, MAGE-A1, -A4, and Rhodopsin E2 (combined as $AR_{high\ risk}$) were significantly associated with shorter overall survival. In HPV-positive patients, antibody responses to IMP-1 were discovered as a negative prognostic factor. $AR_{high\ risk}$ ($HR = 1.76$) and antibody responses to IMP-1 ($HR = 3.28$) were confirmed as independent markers for a poor prognosis in a multivariable Cox proportional hazard model with bootstrapping ($M = 1000$).

Conclusions: We identified antibody responses to cancer antigens that associate with a dismal prognosis in patients with HNSCC beyond HPV-positive status. $AR_{high\ risk}$ may be used to detect HPV-negative patients with an extraordinarily bad prognosis. Most importantly, antibody response to IMP-1 may serve as a marker for a subgroup of HPV-positive patients who present with a poor prognosis similar to that in HPV-negative patients.

Introduction

Globally, head and neck squamous cell carcinoma (HNSCC) is diagnosed in almost 900,000 cases annually resulting in approximately 450,000 cancer-related deaths per year (1). Human papillomavirus (HPV)-positive oropharyngeal squamous cell carcinoma (OPSCC; ref. 2) and head and neck cancer of unknown primary (CUP; ref. 3) have been recognized as distinct entities of HNSCC causally associated with HPV. Clinically, a significant prognostic advantage for HPV-positive OPSCC has been determined in numerous studies for different primary treatment

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Translational Relevance

Human papillomavirus (HPV)-driven head and neck squamous cell carcinoma (HNSCC) is characterized by a much better prognosis than HPV-negative HNSCC. Recent studies focus on deescalation of treatment. However, among HPV-positive patients, a subgroup with a dismal prognosis exists. To prevent harm from treatment deescalation for such patients, biomarkers for high-risk patient identification among HPV-positive patients are needed. We analyzed antibody responses (AR) to nonviral cancer antigens for HPV-positive and HPV-negative patients ($n = 362$) in five independent cohorts treated at large European cancer centers. Antibodies to IMP-1 were associated with reduced overall survival in HPV-positive patients, and antibody responses to c-myc, MAGE-A1, MAGE-A4, and Rhodopsin E2 (combined as $AR_{high\ risk}$) in HPV-negative patients, respectively. Our findings were validated in a multivariable Cox proportional hazard model with bootstrapping (M = 1000). In HPV-positive and -negative HNSCC, antibody responses to cancer antigens may be used to identify high-risk patients.

strategies (4, 5). However, 5-year overall survival (OS) rates of 70%–80% indicate the existence of a subgroup with a dismal prognosis within HPV-positive patients. To date, there is no robust biomarker to detect such patients.

Cancer antigens are immunogenic proteins or peptides that can be recognized by the immune system. Shared cancer antigens include germ-line antigens that are exclusively expressed in tumor tissue such as cancer-testis antigens (6, 7) or cancer-retina antigens (8), oncogenes overexpressed in cancer tissue such as p53 (9), and foreign antigens such as viral antigens (10). Whereas antibody responses (AR) to viral antigens can be used to identify HPV-positive patients (3, 11–14), antibody responses to shared, nonviral antigens may play an important role as prognostic markers in both HPV-positive and HPV-negative HNSCC (15, 16).

The aim of this study was to define the potential prognostic impact of such antibody responses to cancer antigens in patients with HNSCC stratified by HPV status.

Materials and Methods

The study was performed in accordance with the EQUATOR Network CONSORT Guidelines for prognostic studies, namely the Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK Guidelines; ref. 17).

Patients

In this study, 362 patients with curative treatment for histologically diagnosed HNSCC, an available serum or plasma sample taken prior to the initiation of treatment and written informed consent according to the Helsinki Declaration II, were selected. Patients were treated per institutional guidelines at five large head and neck cancer centers, namely University Medical Centers Ulm, Heidelberg Leipzig (Germany), Padua (Italy), and St. Gallen (Switzerland; Supplementary Fig. S1). The American Joint Committee on Cancer, cancer staging manual version 7 was used for classification of tumor–node–metastasis and disease stage.

HPV status

HPV status was determined at each center according to institutional standards. For $n = 294$ patients, a multiplex HPV-DNA PCR ($GP5^+/GP6^+$ primers followed by Sanger sequencing for HPV typing as described previously; ref. 18) and p16 IHC ($n = 254$) was performed. For $n = 146$ patients, HPV E6*I mRNA status (19, 20) was available. Molecular HPV status was considered positive if two of the following three parameters were positive: HPV DNA of known high-risk types, HPV-16 E6*I RNA, and p16 IHC. All other combinations were considered HPV negative. Molecular HPV status showed a significant correlation with the results of HPV serology (Pearson correlation coefficient = 0.775; $P < 0.001$). Thus, for patients lacking data for determination of the molecular HPV status, primarily non-oropharyngeal cancers, results from HPV serology to high-risk types were used as a surrogate parameter resulting in a combined marker HPV (mol/ser).

Material

Serum or plasma samples were prospectively collected prior to treatment initiation, aliquoted, and stored at −20°C until use. Prospective sample collection was in accordance with local ethics committee approvals.

Cancer antigen serology

Full-length proteins of selected cancer antigens were generated for multiplex serology as described previously (21–24). The cancer antigen panel is shown in Table 1.

In brief, genes encoding for 16 cancer-testis antigens, five cancer-retina antigens, eight oncogenes, 29 HPV antigens (from eight high-risk HPV types), and two control antigens (JC and BK virus major capsid protein VP1) were cloned into the pGEX4T3 tag vector for expression in *E. coli* BL21 as fusion proteins with N-terminal glutathione-S-transferase (GST) and a small C-terminal tagging epitope (tag) as described previously (23, 25). GST-tag fusion protein without insert was used to determine serologic background. Anti-GST (GE Healthcare), anti-tag, and anti-mouse

Table 1. Cancer antigen panel for multiplex serology

Cancer-testis antigens ($n = 16$)		**Cancer-retina antigens ($n = 5$)**	Histone H2B	HPV-31 (L1, E6, and E7)
MAGE-A1	SpanXa1	Arrestin	HSP 70	HPV-33 (L1, E6, and E7)
MAGE-A3	SSX2	Recoverin	Ras	HPV-35 (L1, E6, and E7)
MAGE-A4	SSX4	Rhodopsin C	p53	HPV-45 (L1, E6, and E7)
MAGE-A9	IMP1 (IGF2BP1)	Rhodopsin N	pRb	HPV-52 (L1, E6, and E7)
MAGE-C2	cTAGE 5a	Rhodopsin E2	Survivin	HPV-58 (L1, E6, and E7)
CT47	CAMEL	**Oncogenes (nonviral; $n = 8$)**	**HPV-antigens ($n = 29$)**	**Control antigens ($n = 2$)**
GAGE	NY-ESO-1	c-myc	HPV-16 (L1, E6, E7, E1, E2, and E4)	BK virus protein 1
LAGE	OY-TES-1	cyclin D1	HPV-18 (L1, E6, E7, E1, and E2)	JC virus protein 1

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horseradish peroxidase secondary antibodies (Dianova) were used to confirm full-length protein expression and protein integrity.

Multiplex serology was performed as described previously (21–23, 25). For each antigen and bead set, 2,500 glutathione-casein–coated beads per sample were used and sera or plasma were measured at 1:1,000 dilutions. Reporter fluorescence of the beads was determined with the Bio-Plex Analyzer (Bio-Rad) and expressed as mean fluorescence intensity (MFI) of at least 100 beads per set per well. Antigen-specific reactivity was calculated as the difference between antigen-MFI, GST-tag-MFI, and a blank. This value was used for further analyses. Cut-off values were determined graphically for nonviral antigens based on visual inspection of percentile plots (26). For viral antigens, cut-off values were available from previous studies (12).

Statistical analysis

For statistical analysis, the SAMPL guidelines were respected (27). IBM SPSS statistics version 25.0 was used for statistical analysis unless indicated otherwise.

Survival data were available for 360 of 362 patients. OS was defined as the time interval from diagnosis until death. Disease-specific survival (DSS) was defined as the time interval from diagnosis until cancer-related death. Non-cancer–related deaths were not counted as events for DSS. Survival analyses were performed and graphed with SPSS using the Kaplan–Meier method. Analyses with <5 patients in one of the groups analyzed were excluded from OS analysis. Groups were compared by log-rank test. $P < 0.05$ was considered significant, but corrections for multiple testing were performed to reduce statistical errors. Corrections for multiple testing were done using Prism version 7.0c (GraphPad Software, Inc) with a FDR approach for each hypothesis using the two-stage step up method of Benjamini and colleagues (28). Given the exploratory nature of the study, a FDR of up to 15% was tolerated.

Multivariable Cox proportional hazards models were used to calculate HRs and 95% confidence intervals (CI) using R. We applied a bootstrap approach ($M = 1000$) for variable selection (29). This method uses a nested selection procedure over all variable subsets and model comparison via Akaike information criterion to determine the most relevant variables, that is, only the most frequent variables ($\geq$70%) from all bootstrap replications. The following known prognostic markers were included in the multivariable analysis: T status (T1–3, T4, and CUP), N status (N0 and N+), stage (I, II, III, and IV), HPV status (mol/ser), smoking status (yes and no), primary treatment modality (surgical and

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Table 2. Patient characteristics by primary site (oropharynx, CUP, and non-oropharynx)

		Primary site							
		Oropharynx (54.9%)		CUP (11.8%)		Non-oropharynx (44.0%)		Total cohort	
		n	%	*n*	%	*n*	%	*n*	%
Tumor	1	28	14.0%	n.a.	n.a.	22	18.0%	50	13.8%
	2	86	43.0%	n.a.	n.a.	32	26.2%	118	32.6%
	3	35	17.5%	n.a.	n.a.	29	23.8%	64	17.7%
	4	51	25.5%	n.a.	n.a.	39	32.0%	90	24.9%
	Missing	0	0.0%	n.a.	n.a.	0	0.0%	43	11.9%
	Total	200	100%	40	100%	122	100%	362	100%
Node	0	41	20.5%	0	0.0%	61	50.0%	102	28.2%
	1	26	13.0%	15	37.5%	19	15.6%	60	16.6%
	2	125	62.5%	20	50.0%	36	29.5%	181	50.0%
	3	8	4.0%	4	10.0%	6	4.9%	18	5.0%
	Missing	0	0.0%	1	2.5%	0	0.0%	1	0.3%
	Total	200	100%	40	100%	122	100%	362	100%
Metastasis	0	200	100.0%	40	100.0%	122	100.0%	362	100.0%
	Total	200	100%	40	100%	122	100%	362	100%
Stage	I	6	3.0%	0	0.0%	14	11.5%	20	5.5%
	II	17	8.5%	0	0.0%	17	13.9%	34	9.4%
	III	31	15.5%	15	37.5%	30	24.6%	76	21.0%
	IVA/B	146	73.0%	24	60.0%	61	50.0%	231	63.8%
	Missing	0	0.0%	1	2.5%	0	0.0%	1	0.3%
	Total	200	100%	40	100%	122	100%	362	100%
HPV status (mol or ser[a])	HPV^-	77	38.5%	29	72.5%	102	83.6%	208	57.5%
	HPV^+	123	61.5%	11	27.5%	20	16.4%	154	42.5%
	Missing	0	0.0%	0	0.0%	0	0.0%	0	0.0%
	Total	200	100%	40	100%	122	100%	362	100%
Treatment approach	Surgical	148	74.0%	36	90.0%	100	82.0%	284	78.5%
	Nonsurgical	52	26.0%	4	10.0%	20	16.4%	76	21.0%
	Missing	0	0.0%	0	0.0%	2	1.6%	2	0.6%
	Total	200	100%	40	100%	122	100%	362	100%
Sex	Male	151	75.5%	36	90.0%	99	81.1%	286	79.0%
	Female	49	24.5%	4	10.0%	23	18.9%	76	21.0%
	Total	200	100%	40	100%	122	100%	362	100%
Smoking	Nonsmoker	50	25.0%	8	20.0%	30	24.6%	88	24.3%
	Smoker	148	74.0%	30	75.0%	89	73.0%	267	73.8%
	Missing	2	1.0%	2	5.0%	3	2.5%	7	1.9%
	Total	200	100%	40	100%	122	100%	362	100%

Abbreviation: n.a., not applicable.

[a]Molecular HPV status was considered positive if two of three diagnostic tests (HPV RNA, HPV DNA, and p16) were positive. Serology to HPV antigens (compare Table 1) was used whenever molecular status was not available.

nonsurgical), and the primary site (oropharynx, CUP, and non-oropharynx). In addition, all experimental markers that were significantly associated with survival in the whole cohort or stratified by HPV status were integrated into the model.

Results

Patient characteristics of the cohort of 362 patients with HNSCC are presented in Table 2. The majority of patients had an oropharyngeal tumor, explaining the high rate of HPV-positive patients (42.3%). A more detailed description of the patients with non-oropharyngeal tumor is presented in Supplementary Table S1.

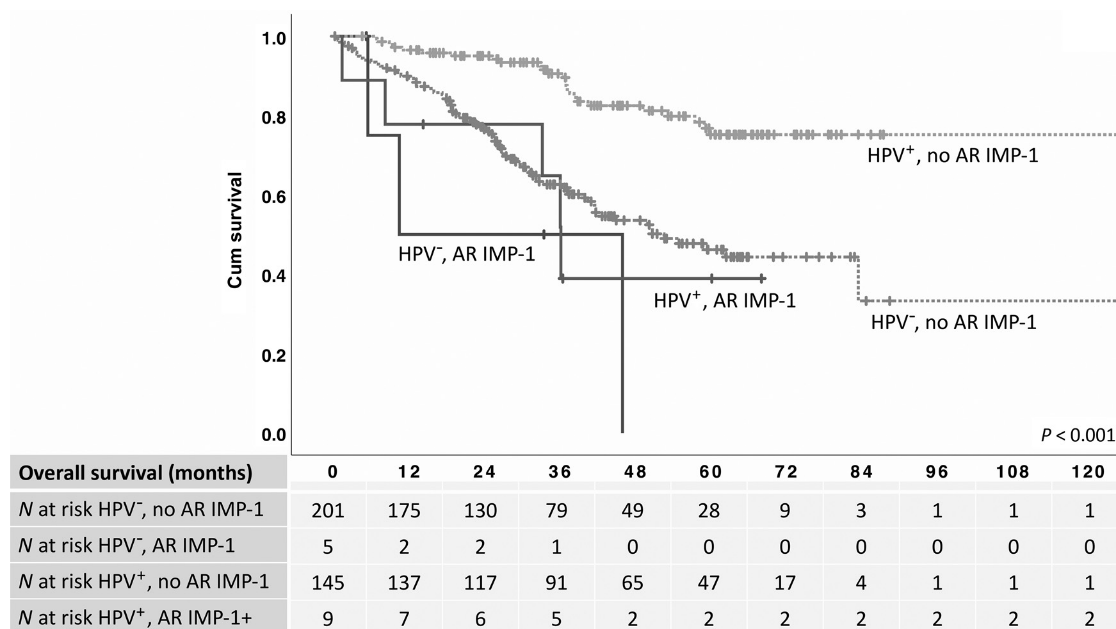
Among the 362 patients, 257 (71%) were seropositive for any of the 29 autoantigens tested. Within the cohort, 360 patients were evaluable for OS and 119 deaths occurred during the follow-up interval. Cause of death was available in 106 of 119 deaths (89%). Among those 106 deaths, 70 (66%) were cancer related.

To identify a prognostic impact associated with the presence of antibody response to certain antigens, OS was analyzed using the Kaplan–Meier method for each of the autoantigens. Patient groups containing <5 patients in one of the groups to be compared were excluded from the analysis. As shown in Supplementary Fig. S1, ≥2 antibody responses, antibody response to IMP-1, MAGE-A1, -A3, -A4, -A9, and p53 Rhodopsin E2 and SSX-2 were associated with significantly shorter OS after correction for multiple testing with a FDR of 15%.

The prognostic impact of HPV status is well-known and can be considered the most important prognostic factor for HNSCC (4, 5, 13). In this cohort, the molecular HPV status, as well as the serologic HPV status (HPV-16 E6 antibodies, antibodies to high risk HPV types), and the combined surrogate marker HPV (mol/ser) resulted in consistent survival differences compared with the respective HPV-negative group (Supplementary Fig. S2). Antibody response patterns and prevalences differed between HPV-positive and HPV-negative patients (not shown). Thus, OS analyses were then performed stratified by HPV status (HPV mol/ser). Interestingly, ≥2 antibody responses to autoantigens, antibody responses to c-myc, MAGE-A1, -A4, and Rhodopsin E2 were significantly associated with shorter OS in HPV-negative patients, but not in HPV-positive patients (Supplementary Fig. S3). On the other hand, antibody response to IMP-1 were significantly associated with shorter OS in HPV-positive patients ($P > 0.001$), but not in HPV-negative patients ($P = 0.150$; Fig. 1). Moreover, HPV-positive patients with antibody response to IMP-1 did not have a significantly different prognosis compared with HPV-negative patients ($P = 0.5$). The results were corrected for multiple testing with a FDR of 15%. Results showed the lowest q value for c-myc in HPV-negative patients ($q < 0.001$) and for IMP-1 in HPV-positive patients ($q < 0.002$).

Antibody response to any antigen with prognostic impact in HPV-negative patients, namely c-myc, MAGE-A1, MAGE-A4, or Rhodopsin E2, were subsequently summarized under a new variable $AR_{high\ risk}$ ($n = 83$). Presence of $AR_{high\ risk}$ was associated with significantly shorter survival in HPV-negative patients compared with patients lacking $AR_{high\ risk}$ or HPV-positive patients ($P < 0.001$; Fig. 2). In HPV-positive patients, no statistical survival difference of patients with $AR_{high\ risk}$ compared with those without $AR_{high\ risk}$ ($P = 0.850$) was found. The results for DSS were not substantially different (not shown).

To address bias from other known prognostic markers, a multivariable Cox proportional hazard model was used. In addition to the known prognostic markers described in the Materials



Overall survival (months)	0	12	24	36	48	60	72	84	96	108	120
N at risk HPV⁻, no AR IMP-1	201	175	130	79	49	28	9	3	1	1	1
N at risk HPV⁻, AR IMP-1	5	2	2	1	0	0	0	0	0	0	0
N at risk HPV⁺, no AR IMP-1	145	137	117	91	65	47	17	4	1	1	1
N at risk HPV⁺, AR IMP-1+	9	7	6	5	2	2	2	2	2	2	2

Figure 1.

Kaplan Meier plots are shown for human papillomavirus (HPV)-positive and HPV-negative patients with or without antibody responses (AR) to IMP-1. HPV^+/AR IMP-1 patients (mean OS 41.2 months) had a much shorter overall survival than HPV+/no AR IMP-1 patients (mean OS 109.3 months, $P < 0.001$). In fact, HPV+/AR IMP-1 patients (mean OS 41.2 months) had a similar prognosis to HPV^-/no AR IMP-1 patients (mean OS 27.0 months, $P = 0.530$) or HPV^-/AR IMP-1 patients (79.7 months, $P = 0.515$).

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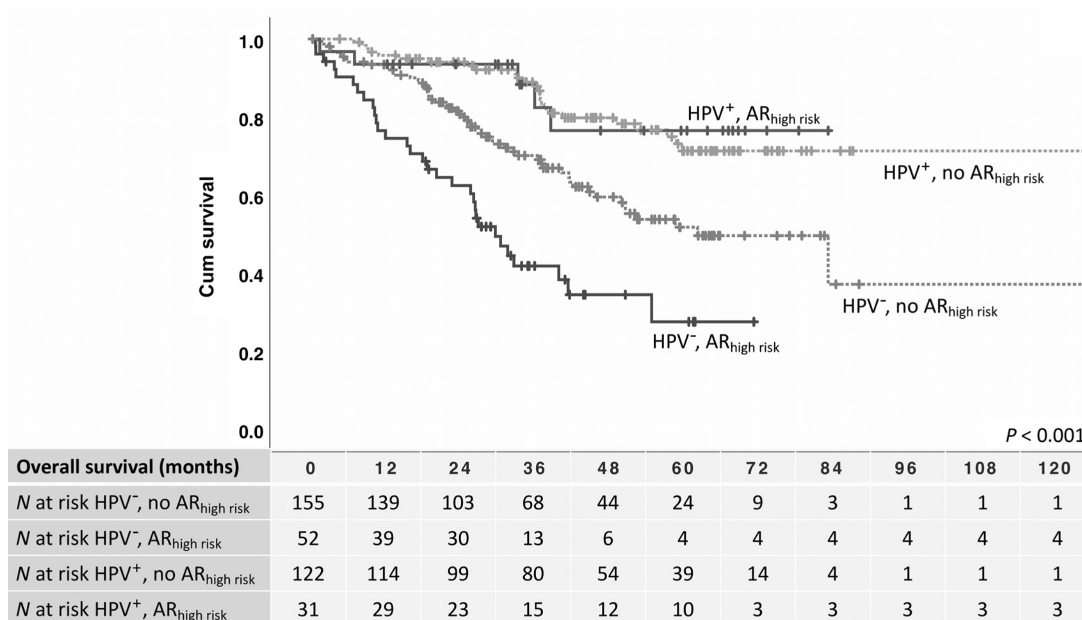

Figure 2.

OS of patients with antibody responses to $AR_{high\ risk}$. Antibody responses (AR) to c-myc, MAGE-A1, -A4, or Rhodopsin E2 were summarized under the variable $AR_{high\ risk}$. Kaplan–Meier plots are shown for HPV-positive and HPV-negative patients with or without antibody responses ($AR_{high\ risk}$). $HPV^-/AR_{high\ risk}$ patients (mean OS 36.5 months) had a significantly shorter OS than HPV^-/no $AR_{high\ risk}$ patients (mean OS 87.3 months; $P < 0.001$), HPV^+/no $AR_{high\ risk}$ patients (mean OS 105.5 months; $P < 0.001$), or $HPV^+/AR_{high\ risk}$ patients (mean OS 70.3 months; $P < 0.001$).

and Methods section, all antibody responses with a potential prognostic impact based on the OS analysis in the different patient groups (all, HPV positive, and HPV negative) were tested, namely MAGE-A3 antibody response (AR^- and AR^+), MAGE-A9 antibody response (AR^- and AR^+), p53 antibody response (AR^- and AR^+), SSX2 antibody response (AR^- and AR^+), $AR_{high\ risk}$, IMP1 antibody response (AR^- and AR^+), and the number of antibody response (0–1 and ≧2). In the final model, advanced T category, $AR_{high\ risk}$, and antibody response to IMP-1 were associated with a significantly increased HR, whereas HPV-positive status was associated with a significantly reduced HR (Cox proportional hazard model; Wald: $P = 6e\text{-}11$). HR values for the four variables in the final model with the respective 95% CIs, P values, and the number of positive bootstraps are listed in Table 3.

Discussion

We were able to show a significant prognostic impact for shorter OS associated with several antibody response to cancer antigens, both agnostic of and stratified by HPV status. The multivariable Cox proportional hazard models confirmed $AR_{high\ risk}$ and IMP-1 among T category and HPV status ($HPV_{mol/ser}$) as independent markers of a poor prognosis. Instead of arbitrarily dividing the cohort from the five centers into just one test and one validation cohort, we selected a bootstrap approach ($M = 1000$) for variable selection (29). The benefit of this method is a nested selection procedure over all variable subsets. All models were compared via Akaike information criterion to determine the most relevant variables. Only the most frequent variables (>=70%) from all bootstrap replications were selected for the final model. $AR_{high\ risk}$ and IMP-1 were stably presented variables in the 1000 models tested.

Thus, we have identified a serologic marker, each to detect patients at higher risk of death, for HPV-negative patients ($AR_{high\ risk}$) and for HPV-positive patients (IMP-1).

IMP-1 (insulin-like growth factor 2 mRNA-binding protein 1; IGF2BP1) is a mRNA binding protein that functions as a transcription factor and also belongs to the cancer-testis antigen

Table 3. Final multivariable Cox proportional hazard model based on 1000 bootstraps

		HR (95% CI)	P	Positive bootstrap replicates
T status	T1–3	1		791
	T4	1.750 (1.158–2.644)	0.008	
	CUP	2.460 (1.420–4.261)	0.001	
HPV status (mol/ser)	HPV^-	1	<0.0001	1000
	HPV^+	0.340 (0.222–0.521)		
$AR_{high\ risk}$	AR^-	1	0.007	716
	AR^+	1.756 (1.167–2.642)		
IMP-1 antibody response	AR^-	1	0.002	859
	AR^+	3.279 (1.562–6.882)		

NOTE: Parameters in the model initially (1000 bootstraps): T status (T1–3, T4, and CUP), N status (N0 and N+), stage (I, II, III, and IV), HPV status (mol/ser), smoking status (yes and no), primary therapy (surgical and nonsurgical), primary site (oropharynx, CUP, and non-oropharynx), MAGE-A3 antibody response (AR^-, AR^+), MAGE-A9 antibody response (AR^-, AR^+), p53 antibody response (AR^-, AR^+), SSX2 antibody response (AR^-, AR^+), antibody response HPV-negative, IMP1 antibody response (AR^-, AR^+), and antibody response number (0–1, ≧2).

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family (30). By binding to mRNA it forms a protein–mRNA complex, which stabilizes the target RNA and enhances translation of protein, for example, of c-myc (31) or KRAS (32). It is considered to promote cell proliferation and tumorigenesis (31, 33, 34) and has been associated with a poor prognosis in neuroblastoma (35). Humoral immune responses to IMP-1 have previously been described in ovarian cancer (30).

Within the group of HPV-positive patients, a biomarker to identify those HPV-positive patients who have a prognosis comparable with HPV-negative patients is lacking. Smoking status has been reported as a prognostic marker for HPV-positive patients (4), but was not associated with a poor prognosis in our multivariable model. This may be due to different smoking habits in Germany. German HPV-positive patients tend to have a smoking history above 10-pack years in the median (36). In view of efforts to deescalate treatment for HPV-positive patients, it is highly important to detect high-risk patients.

Recently, two treatment deescalation trials for HPV-positive patients were published, both only using p16 for determination of HPV status (37, 38). In contrast to the expected outcome, both trials failed to prove that cetuximab is less toxic than high-dose cisplatin. Instead exchanging cisplatin for cetuximab had a detrimental impact on OS.

Alarmingly, in the clinical routine in the United States, some physicians are not recommending adjuvant treatment to surgically treated HPV-positive patients (39). To protect HPV-positive patients with a bad outcome from harm, the subgroup of patients with a poor prognosis needs to be identified, if a deescalation of treatment for HPV-positive patients should be established in the future.

Several other studies have associated antibody response to certain cancer antigens with detrimental or beneficial prognosis (22, 24, 40). In most studies and for most antigens, a negative prognostic impact, consistent with our results, was found. These findings indicate that humoral immunity to cancer antigens may be a poor surrogate marker for active cancer immunity, but rather an indirect measure of antigen expression as shown previously (40–43). At the same time, these patients may be candidates for antigen-specific immunotherapy, which may improve the detrimental outcome. Cancer antigen serology may therefore identify patients who are at high risk of death, but who may benefit from immunotherapy (44).

There are some limitations to our study: patients were not treated within a prospective clinical trial with a defined treatment regimen. However, patients were treated at five large European cancer centers in line with international treatment guidelines. Because of the number of hypotheses tested, corrections for multiple testing were needed and performed. Some of the prognostic groups compared were rather small due to the diversity of antibody response patterns. However, the results for $AR_{high\ risk}$ and IMP-1 remained stable up to a FDR of 1%. The multivariable Cox proportional hazard model with 1000 bootstraps also confirmed these two factors among T category and HPV status to be significantly correlated with OS. The prognostic impact of serologic antibodies detected at baseline is somewhat controversial (3, 22, 24, 45, 46). Antibody levels and biological activity may change over the course of the disease. As such, cancer-antigen antibodies may represent an interesting biomarker during post-treatment surveillance. However, a prospective validation of these new markers, preferably in a randomized trial with samples taken over the course of treatment and follow-up would be desirable.

In conclusion, our results show that $AR_{high\ risk}$ may be used to identify patients with a dismal prognosis among HPV-negative patients and antibody response to IMP-1 among HPV-positive patients. Antibody response to IMP-1 is a novel marker to detect HPV-positive patients who have a comparable prognosis to HPV-negative patients. In view of current strategies to deescalate treatment for HPV-positive patients (39) such patients are at risk and need to be identified.

Disclosure of Potential Conflicts of Interest

S. Laban reports receiving speakers bureau honoraria from MSD, AstraZeneca, Bristol-Myers Squibb, and Merck Serono, and is a consultant/advisory board member for MSD, Bristol-Myers Squibb, and AstraZeneca. P.J. Schuler reports receiving speakers bureau honoraria from Advisory Boards. No potential conflicts of interest were disclosed by the other authors.

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