Human Papillomavirus Drives Tumor Development Throughout the Head and Neck: Improved Prognosis Is Associated With an Immune Response Largely Restricted to the Oropharynx


ABSTRACT

Purpose
In squamous cell carcinomas of the head and neck (HNSCC), the increasing incidence of oropharyngeal squamous cell carcinomas (OPSCCs) is attributable to human papillomavirus (HPV) infection. Despite commonly presenting at late stage, HPV-driven OPSCCs are associated with improved prognosis compared with HPV-negative disease. HPV DNA is also detectable in non-oropharyngeal (non-OPSCC), but its pathogenic role and clinical significance are unclear. The objectives of this study were to determine whether HPV plays a causal role in non-OPSCC and to investigate whether HPV confers a survival benefit in these tumors.

Methods
Meta-analysis was used to build a cross-tissue gene-expression signature for HPV-driven cancer. Classifiers trained by machine-learning approaches were used to predict the HPV status of 520 HNSCCs profiled by The Cancer Genome Atlas project. DNA methylation data were similarly used to classify 464 HNSCCs and these analyses were integrated with genomic, histopathology, and survival data to permit a comprehensive comparison of HPV transcript-positive OPSCC and non-OPSCC.

Results
HPV-driven tumors accounted for 4.1% of non-OPSCCs. Regardless of anatomic site, HPV+ HNSCCs shared highly similar gene expression and DNA methylation profiles; nonkeratinizing, basoloid histopathological features; and lack of TP53 or CDKN2A alterations. Improved overall survival, however, was largely restricted to HPV-driven OPSCCs, which were associated with increased levels of tumor-infiltrating lymphocytes compared with HPV-driven non-OPSCCs.

Conclusion
Our analysis identified a causal role for HPV in transcript-positive non-OPSCCs throughout the head and neck. Notably, however, HPV-driven non-OPSCCs display a distinct immune microenvironment and clinical behavior compared with HPV-driven OPSCCs.

INTRODUCTION

High-risk human papillomaviruses (hrHPVs) infect mucosal epithelia and cause carcinomas at several anogenital sites, accounting for almost all cervical cancer cases worldwide.1 HPV is also a strong independent risk factor for oropharyngeal squamous cell carcinoma (OPSCC), a subset of head and neck cancers that occur in the epithelial lining lymphoid crypts of the tonsils and tongue base.2 Head and neck squamous cell carcinomas (HNSCCs, including those OPSCCs unrelated to HPV) typically occur in patients older than 60 years with a history of heavy smoking and high alcohol intake; HPV-driven OPSCCs affect a younger population, with a median age at diagnosis of younger than 60 years and often with little or no smoking history.3 Rates of HPV-negative (HPV−) HNSCC have begun to decline in the United States, Europe, and Australia; by contrast, HPV-driven OPSCC incidence...
is rapidly increasing in these countries. Although prophylactic vaccination against hrHPV types has the potential to prevent HPV-driven OPSCC, the sustained lifetime risk of oral hrHPV infection, coupled with a later age at diagnosis than cervical cancer, has led to the prediction that it will be at least 2060 before the current rising trend is reversed, emphasizing the need to correctly diagnose and treat these tumors. The clinical behavior of HPV-driven OPSCC also differs from HPV− disease, having significantly better progression-free and overall survival. These observations have led to HPV status becoming a routine molecular test for patients with OPSCC, and also with the aggressive chemoradiotherapy regimens used for HNSCC.

Meta-Analysis Defines a Cross-Tissue Transcriptional Signature for HPV-Driven Carcinogenesis

We conducted a meta-analysis of seven gene expression microarray (U133A, U133+2) studies that included tissue samples and cell-line models representing normal epithelium (n = 69), HPV− (n = 55), and HPV-driven (n = 138) tumors (Data Supplement Table A1). Effect size combination was used to account for cross-study/cross-platform batch effects.

A total of 159 genes were differentially expressed in the HPV-driven samples (false discovery rate [FDR] < 0.01; greater than two-fold change; Data Supplement Table A2). Differentially expressed gene (DEG) signature members showed a consistent pattern of deregulation across the datasets, as visualized by clustering (Clustering Index: range, 0% to 4.2%; Fig 1; Data Supplement Methods). Signature gene expression was also stronger in late passage/transformed HPV+ keratinocytes than in cells profiled immediately after HPV16 infection (Data Supplement Fig A1A).

Furthermore, analysis of a gene expression dataset from mesenchymal stem cells transduced with E6 and/or E7 demonstrated that the signature genes were modulated by HPV oncogenes not only in a cross-tissue fashion but also in different cellular lineages (Data Supplement Fig A1B).

The 159 DEG Signature Serves as a Functional Readout for HPV Oncogene Activity

Consistent with published gene expression signatures for HPV-associated cancers placing our DEG signature genes in a functional context using Ingenuity Pathway Analysis (Qiagen, Redwood City, CA) revealed expression changes consistent with remodeling of cell cycle progression by E7; notably CDKN2A and CCNE overexpression and CCND1 downregulation (Data Supplement Fig A2). Upstream regulatory analysis indicated inhibition of p53 and activation of E2F, again consistent with the well-characterized actions of the HPV oncoproteins on these pathways (Data Supplement Table A3). The 159-DEG signature also contains multiple genes previously found to be dysregulated in HPV-associated cancers, such as the meiotic synaptonemal complex component SYCP2, members of the replication licensing complex and kallikrein genes. Taken together, the expression signature reflects a causal role for HPV in these tumors.

HPV Transcript-Positive OPSCC and Non-OPSCC Share Common Gene Expression Patterns

Next, we analyzed TCGA HNSC dataset, for which RNA-sequencing data are now available from 520 samples. We detected HPV transcripts in 54 of 80 OPSCC samples (67.5%) and 21 of 440 non-OPSCCs (4.8%); these are termed HPV+ (Data Supplement Table A4). Of the 159 expression signature genes, 127 were differentially expressed between HPV+ and HPV− samples (FDR < 0.01) in this data set. Almost all HPV+ samples (69 of 75) clustered together regardless of anatomic subsite, with OPSCCs and non-OPSCCs interspersed (Fig 2A).

To test whether this gene set can accurately predict HPV status, we used two machine-learning approaches (the k-Nearest
Neighbors [k-NN] algorithm and Random Forests [RF]; Salford Systems, San Diego, CA) to build classifiers. Both models performed well, returning out-of-fold kappa values (a measure of classifier accuracy) of 0.96 by RF and 0.94 by k-NN. The RF model correctly predicted all 445 HPV+ tumors and misclassified four of 75 HPV+ tumors (three non-OPSCC, one OPSCC), whereas the k-NN model misclassified four HPV+ and three HPV+ tumors. Thus, the HPV status of OPSCCs and non-OPSCCs can be predicted using classifiers based upon our 159-DEG signature.

**HPV Transcript-Positive OPSCC and Non-OPSCC Display Similar Genome-Wide DNA Methylation Landscapes**

In addition to characteristic gene expression changes, several studies have reported distinct DNA methylation profiles between HPV+ and HPV− OPSCC, with HPV+ OPSCCs more closely resembling HPV+ cervical cancers than either HPV− OPSCC or lung squamous carcinoma.31-33 Using genome-wide DNA methylation profiles for only TCGA OPSCC samples (50 HPV+, 20 HPV−), we defined a 468-methylation variable position (MVP) signature (change in β [delta beta; dB] ≥ 0.4; FDR < 0.001; Data Supplement Table A5). When applied to the entire data set, this MVP signature clustered 60 of 69 HPV+ HNSCCs together, regardless of anatomic subsite (Fig 2B) and classifiers built using k-NN (κ = 0.93; none of 395 HPV− and seven of 69 HPV+ tumors misclassified) or RF (κ = 0.92; two of 395 HPV− samples, seven of 69 HPV+ samples misclassified) were able to predict the HPV status of non-OPSCCs as well as OPSCCs. These results support the conclusions, on the basis of gene expression data, that HPV+ OPSCCs and non-OPSCCs are molecularly similar and distinguishable from HPV− HNSCCs. These similarities in transcriptome and methylome profiles are further evident when visualized on multidimensional scaling plots (Data Supplement Fig A3). No MVPs differed between HPV+ OPSCC and HPV+ non-OPSCC at an FDR of 0.01/dB > 0.4, and only 19 differed at dB > 0.3.

**HPV Oncogene Transcript Levels Do Not Vary Between HPV+ OPSCC and Non-OPSCC**

Expression of the E6 and E7 viral oncogenes increases during HPV-driven tumor development and cells from these tumors are dependent on their continued expression. Assuming that if the HPV− non-OPSCCs are, indeed, HPV-driven, they should express comparable E6/E7 levels as the HPV+ OPSCCs. We compared the levels of these transcripts and observed no difference between the two groups (Fig 2C). HPV+ non-OPSCCs, therefore, clearly

![Fig 1. Human papillomavirus (HPV)-driven tumors display a common gene expression signature. Meta-analysis identified 179 probes mapping to 159 gene probes as being significantly differentially expressed between HPV+ tumors and HPV− controls (tumor or normal). Annotations represent sample type data where relevant, and HPV status. CESC, cervical squamous cell carcinoma; HNSCC, squamous cell carcinoma of the head and neck; VIN, vulval intraepithelial neoplasia.](image)
express levels of E6 and E7 sufficient for the growth and survival of known HPV-driven tumors.

**Genomic Similarities Between HPV+ OPSCC and Non-OPSCC**

Having observed strong similarities between HPV+ OPSCC and non-OPSCC at the gene expression and epigenetic levels, we next examined the genomic features of these tumors. We previously reported elevated fractions of mutations attributable to deoxycytidine deaminase (APOBEC) activity in HPV+ HNSCC.\(^{34}\) Furthermore, APOBEC3B, previously implicated in this mutational process,\(^{35}\) was part of our gene expression signature (Data Supplement Table A2). The larger set of 502 HNSCCs that have now been exome sequenced by TCGA (including 68 HPV+) allowed us to compare enrichment for APOBEC signature mutations (C\( \rightarrow \)T or C\( \rightarrow \)G mutations occurring within the TCW trinucleotide motif, where W = A or T) in OPSCC versus non-OPSCC (Data Supplement Fig A4). Controlling for smoking history (which defines a separate subgroup within HPV+ OPSCC with respect to survival and APOBEC signature mutations\(^{36,37}\)), HPV status remains a strong predictor for APOBEC independent of anatomic site (odds ratio, 3.07; \(P < 2.2 \times 10^{-16}\)), with HPV+ non-OPSCCs displaying an even higher proportion of APOBEC signature mutations than HPV+ OPSCC (odds ratio, 1.29; \(P = 2.2 \times 10^{-9}\)), again consistent with an HPV-driven etiology.

In addition to differences in global mutational signatures, HPV− and HPV+ OPSCCs display characteristic mutations and/or copy number alterations. TP53, CDKN2A, and CCND1 alterations are almost exclusive to HPV− OPSCCs, in which they occur at high frequency.\(^ {31,38-41}\) In HPV+ OPSCCs, E6-mediated p53 degradation removes selection pressure for TP53 mutations, and bypass of the G1/S checkpoint by E7 likewise obviates pressure to acquire CDKN2A or CCND1 alterations.\(^ {40,42}\) As expected, we observed high frequencies of TP53 mutations, CDKN2A mutations, deletions, and CCND1 amplifications in HPV− HNSCCs, and very low frequencies of these alterations in HPV+ OPSCC. Again, HPV+ non-OPSCC tumors closely resembled HPV+ OPSCCs (Table 1). Taken together, our molecular analyses strongly implicated HPV as a driver in 72 of 75 transcript-positive HNSCCs, and subsequent analyses focused on these tumors, hereafter termed HPV-driven (Data Supplement Methods).
**HPV-Driven Non-OPSCCs Frequently Display the Basaloid Morphology Typical of HPV-Driven OPSCCs**

To complement our molecular observations, we conducted histopathological analysis, grading those TCGA cases for which evaluable images of H&E-stained sections were available through TCGA Digital Image Archive. As expected, the majority (39 of 41) HPV+ OPSCC cases displayed a characteristic basaloid (poorly differentiated) morphology, which has previously been linked to their origin in nonkeratinizing tonsillar crypt epithelium. Strikingly, whereas HNSCCs arising at other sites are typically keratinizing (well to moderately differentiated), 11 of the evaluable 15 HPV+ non-OPSCCs also displayed the basaloid morphology characteristic of the OPSCCs (Data Supplement Table A6). Consistent with these observations, comparison of global cytokeratin gene expression profiles revealed an intermediate pattern in the HPV-driven non-OPSCCs, suggesting they are determined by a combination of both HPV and anatomic site (Data Supplement Fig A5).

**HPV-Driven Tumors Show Different Prognosis by Anatomic Subsite**

Patients with OPSCC with an HPV etiology show significantly improved survival compared with those with HPV− disease.5,6 Having demonstrated that HPV plays a causative role in transcript-positive non-OPSCC, we examined whether patients with these tumors display a similarly favorable prognosis. Kaplan-Meier analysis of TCGA cohort stratified into four groups by tumor HPV status and anatomic subsite suggested improved overall survival (OS) specifically in HPV-driven OPSCC (Fig 3). Accordingly,

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**Table 1. Hallmark Genomic Alterations by Anatomic Site and HPV Status**

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<thead>
<tr>
<th>Group</th>
<th>TP53 Mutation</th>
<th>CDKN2A Mutation</th>
<th>CCND1 Amplification</th>
<th>CDKN2A Deletion</th>
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<tr>
<td>HPV+ OPSCC</td>
<td>0 of 50 (0)</td>
<td>0 of 50 (0)</td>
<td>6 of 54 (11.1)</td>
<td>4 of 54 (7.4)</td>
</tr>
<tr>
<td>HPV+ non-OPSCC</td>
<td>1 of 18 (5.5)</td>
<td>0 of 18 (0)</td>
<td>3 of 21 (14.2)</td>
<td>3 of 21 (14.2)</td>
</tr>
<tr>
<td>HPV− OPSCC</td>
<td>23 of 25 (92%)</td>
<td>5 of 25 (20)</td>
<td>19 of 26 (73.7)</td>
<td>22 of 26 (84)</td>
</tr>
<tr>
<td>HPV− non-OPSCC</td>
<td>336 of 409 (82%)</td>
<td>107 of 409 (26)</td>
<td>197 of 413 (47.6)</td>
<td>281 of 413 (68)</td>
</tr>
</tbody>
</table>

NOTE: Data given as proportion (%).
Abbreviations: HPV, human papillomavirus; OPSCC, oropharyngeal squamous cell carcinoma.
*Proportions represent number of samples with genomic alteration out of total samples with data available.
**Anatomic Subsite Is Associated With Differences in Lymphocyte Infiltration and Activation**

In addition to age, stage, and smoking history, TIL levels are reported to be associated with survival in HPV-driven OPSCC, with low TIL numbers identifying a subgroup of patients with poor prognosis and similar survival rates to those with HPV−OPSCCs. The importance of the immune system in shaping the evolution of HPV-driven OPSCC is also reflected by the high levels of programmed death ligand 1 expressed by these tumors. Therefore, we compared TIL levels between HPV-driven OPSCC and non-OPSCC by measuring CD4 (helper/ regulatory T lymphocyte) and CD8A/CD8B (cytotoxic T lymphocyte) mRNA abundance; we found significantly higher levels of both mRNAs in OPSCC (Fig 4A). Consistent with this, we also observed increased TILs in H&E-stained sections from HPV-driven OPSCCs (Cochran-Armitage trend test, \( P = .046 \); Data Supplement Table A6) and found increased expression of multiple T-cell effector markers in HPV-driven OPSCC (Data Supplement Fig A6).

Given the importance of immune checkpoint in modulating antitumor immune responses and the observation that PD1-expressing TILs are associated with favorable prognosis in HPV-driven OPSCC, we next investigated the clinical impact of TIL levels and their effector and immune checkpoint activity. Clustering HPV-driven tumors on the basis of their expression of a panel of T-cell genes denoting lineage, activation, and immune checkpoint expression revealed two clusters (Fig 4B). The low expression (immune-depleted) cluster was strongly enriched for non-OPSCCs (14 of 18 non-OPSCGs and 18 of 54 OPSCCs), with immune enrichment associated with longer OS in multivariable analysis (Fig 4C; Table 2). Finally, we examined relationships between the HPV-driven tumors and a previously published gene co-expression module (M1) enriched for genes associated with CD8+ T cells and improved survival in HNSCC (Fig 4D).

Gene expression in TIL-high HPV-driven tumors was correlated with this module (\( r = 0.46; 95\% \text{ CI}, 0.44 \text{ to } 0.49; P < 2.2 \times 10^{-16} \)), HPV-driven non-OPSCCs, however, were inversely correlated with M1 (\( r = -0.65; 95\% \text{ CI}, -0.67 \text{ to } -0.63; P < 2.2 \times 10^{-16} \) and were, instead, mostly correlated (\( r = 0.66; 95\% \text{ CI}, 0.64 \text{ to } 0.67; P < 2.2 \times 10^{-16} \)) with a module (M2) associated with upregulated glucose metabolism and poor outcome, overrepresented in tumors of the basal subtype not previously linked to HPV-driven HNSCC.

Overall, the HPV-driven OPSCCs and non-OPSCCs were very similar; we found only 67 DEGs (Data Supplement Table A7) and no significant MVPs. However, taken together, our analyses reveal a clear, survival-associated difference in lymphocyte infiltration between HPV-driven OPSCC and non-OPSCC.

**DISCUSSION**

The importance of HPV in OPSCC and its implications for patient treatment and the design of clinical trials are well established. HPV is detected at lower frequencies in non-OPSCC, where its biologic role and clinical relevance are unclear. We hypothesized that if HPV were playing a driver role in these tumors, they would share molecular profiles of known HPV-driven cancers. Our study shows that HPV−non-OPSCCs do, indeed, share a gene expression signature consistent with an HPV-driven etiology. Furthermore, HPV−HNSCCs are similar (and distinct from HPV−HNSCCs) at the epigenetic and genomic levels. HPV+ non-OPSCCs also frequently display the basaloid morphology that characterizes HPV+ OPSCC. This finding, also supported by observations from HPV-associated anogenital and sinonasal cancers, is consistent with a role for HPV.
in blocking the differentiation of cells that would normally give rise to keratinizing epithelia.51,52

Our findings suggest that viral etiology alone is insufficient to confer favorable prognosis in HNSCC and that this effect is largely limited to the oropharynx; among non-OPSCC cases, any survival benefit of HPV seems minimal (hazard ratio, 0.82; 95% CI, 0.38 to 1.76; \(P = .63\)). These findings are supported by two previous studies, in which p16 expression in non-OPSCC was associated with either a more limited or no improvement in OS.8,10  We acknowledge that given the possible heterogeneity between tumors from different anatomic head and neck subsites, it is not ideal to class “non-OPSCC” as a single group—a fact also accepted by Chung and colleagues8 as a limitation in their prognostic analysis of p16 expression in non-OPSCC. We also recognize that although we see a clear difference in OS and lymphocyte infiltration and activity between HPV-driven

Fig 4. Enhanced lymphocyte infiltration in HPV-driven OPSCC. (A) Variance stabilization transformed mRNA levels of TIL markers CD4, CD8A, and CD8B. Each was significant at a false discover rate < 0.05 (Wilcoxon’s rank-sum test) comparing HPV-driven OPSCC with HPV-driven non-OPSCC. (B) The expression heat map of immune checkpoint gene transcripts highlights a low expression and a moderate/high expression cluster within HPV-driven squamous carcinoma of the head and neck (HNSCC); annotation bars represent anatomic subsite and cluster allocation from consensus clustering. (C) Kaplan-Meier curve of HPV+ HNSCC stratified by TIL status. The table represents the number at risk at the given time points. Statistics are from multivariable Cox regression controlling for age, smoking history (more or fewer than 10 pack-years), subsite, T stage (T1/2 v T3/4) and N stage (N0-N2a v N2b-N3). This also is compared in Table 2. (D) Weighted correlation network analysis network graphs. Each gene is labeled by color according to correlation with the indicated tumor subtype. Red and blue show positive and negative correlation, respectively. HPV, human papillomavirus; Neg, negative; OPSCC: oropharyngeal squamous cell carcinoma; Oro, oropharyngeal; Pos, positive; TIL, tumor-infiltrating lymphocyte.
OPSCC and non-OPSCC, there were insufficient data on treatment in this cohort to permit its inclusion as a variable in multivariable analysis. Investigation of a larger, uniformly treated patient cohort is needed, therefore, to confirm that the difference in prognosis is independent of possible differences in patient management between OPSCC and non-OPSCC. Notably, in OPSCC, the improved prognosis of patients with HPV-driven disease has been shown in several studies to be independent of treatment modality, arguing for a tumor-intrinsic factor in driving this survival difference. It has been suggested that this is due, at least in part, to increased radiosensitivity, perhaps resulting from retention of wild-type TP53. The almost universal retention of wild-type TP53 in HPV-driven HNSCC (Table 1) suggests an alternative explanation for the survival difference by subsite.

The difference in TIL levels between HPV-driven OPSCC and non-OPSCC suggests a fundamentally different immune response to these tumors. Interestingly, in their analysis of the initial HNSCC dataset of 279 tumors, 14 of which were HPV transcript-positive non-OPSCCs, TCGA classified several as belonging to the basal transcriptional subtype initially identified by Chung and colleagues. Our analysis demonstrates that these tumors are, in fact, highly similar to HPV-driven OPSCCs of the atypical subtype, and that they are also HPV-driven but lack the lymphocyte infiltration associated with improved outcomes in OPSCC. This observation potentially explains the survival differences between HPV-driven tumors at these sites and implies that there is something unique to the oropharynx that enhances the immune response to HPV-driven tumors (but not HPV− tumors) arising at this location.

Our analysis identifies and provides important insight into a new patient population, with implications for both cancer prevention and treatment. Using multiomic TCGA data has uniquely allowed us to build a comprehensive molecular map of HPV+ HNSCCs and to use HPV transcript detection as our marker for HPV positivity throughout, thus identifying a significant role for HPV outside the oropharynx and avoiding the previously documented pitfalls of either HPV DNA or p16 detection. HPV transcript-positive non-OPSCCs are HPV driven and would likely benefit from HPV-targeted therapies (and be prevented by prophylactic HPV vaccination). The relatively poor prognosis
of HPV-driven non-OPSCC, however, argues against treatment de-escalation for these tumors, whereas clear differences in the immune microenvironment suggest we may expect altered responses to immune checkpoint blockade. From a precision medicine perspective, HPV-driven non-OPSCC cases should be identified and considered as a distinct entity with respect to both HPV− HNSCC and HPV-driven OPSCC.

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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<table>
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<th>Author</th>
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</tr>
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<tbody>
<tr>
<td>Ankur Chakravarthy</td>
<td>No relationship to disclose</td>
</tr>
<tr>
<td>Stephen Henderson</td>
<td>No relationship to disclose</td>
</tr>
<tr>
<td>Stephen M. Thirdborough</td>
<td>No relationship to disclose</td>
</tr>
<tr>
<td>Christian H. Ottensmeier</td>
<td></td>
</tr>
<tr>
<td><strong>Speakers’ Bureau:</strong></td>
<td>Bristol-Myers Squibb, Roche, Delcath Systems</td>
</tr>
<tr>
<td><strong>Research Funding:</strong></td>
<td>Bristol-Myers Squibb (Inst), Amgen (Inst), Asterias (Inst), BioNTech AG (Inst), MedImmune (Inst), MSD (Inst), Touchlight Genetics (Inst), Verastem (Inst)</td>
</tr>
<tr>
<td>Xiaoping Su</td>
<td>No relationship to disclose</td>
</tr>
<tr>
<td>Matt Lechner</td>
<td>No relationship to disclose</td>
</tr>
<tr>
<td>Andrew Feber</td>
<td>No relationship to disclose</td>
</tr>
<tr>
<td>Gareth J. Thomas</td>
<td>Consulting or Advisory Role: GlaxoSmithKline, MSD</td>
</tr>
<tr>
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