HPV and prognosis for patients with oropharynx cancer

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Tumour HPV status is an important predictor of overall and disease-specific survival for patients with oropharynx squamous cell carcinoma. The potential prognostic significance of HPV in head and neck cancer was originally suggested in single-institutional case-series, the majority of which reported tumour HPV status to be a favourable biomarker for survival outcomes, particularly for oropharyngeal cancers. In these original reports, patients with HPV-positive tumours were estimated to have a 50–80% reduction in risk of disease-failure when compared to the HPV-negative patient [1–4]. Despite the significant heterogeneity in patient populations (with regard to sample size, methods for tumour HPV classification, tumour stage, tumour treatment, and variable inclusion of other prognostic factors in the analysis) HPV has been consistently associated with more favourable outcomes in these studies.

In a recent meta-analysis of these case-series [5], patients with HPV-positive head and neck squamous cell carcinomas had an 18% (hazard ratio (HR) 0.85, 95% confidence interval (CI) 0.7–1.0) reduction in risk of death and a 38% (HR 0.62, 95% CI 0.5–0.8) reduction in risk of disease-failure when compared to the HPV-negative patient. When stratified by anatomic site of the primary tumour, the survival benefit was restricted to HPV-positive oropharyngeal cancers. Patients with HPV-positive oropharyngeal cancers were estimated to have a 28% (HR 0.72, 95% CI 0.5–1.0) reduced risk of death and a 49% (HR 0.51, 95% CI 0.4–0.7) reduced risk of disease-failure when compared to patients with HPV-negative oropharyngeal cancers. This meta-analysis had some limitations, as the estimates were derived from un-adjusted hazards and were not based on individual patient data. Additionally, no attempt was made to classify studies based upon method used for tumour HPV classification, categorisation likely resulting in false-positive classification which would bias results toward the null. However, the inclusion of patients with recurrent or metastatic disease in the survival analysis may have biased results away from the null, by worsening survival outcomes preferentially in the HPV-negative group. Nevertheless, the meta-analysis is a useful summary of the existing literature from retrospective, case-series.

Because of the initial reports noted above, the Eastern Cooperative Oncology Group (ECOG) incorporated an analysis of the effect of tumour HPV status on survival outcomes in a phase II trial of investigational therapy in patients with oropharyngeal and laryngeal cancers, ECOG 2399 [6]. In this trial, patients were treated with paclitaxel and carboplatin induction followed by radiation concurrently administered with weekly radiosensitising paclitaxel. Tumour HPV status was determined via a combination of HPV *in situ* hybridisation and polymerase chain reaction (PCR), and 40% of all cancers and 63% of oropharyngeal cancers were found to be positive. After a median survival of 39 months, patients with HPV-positive tumours had an improved overall survival and after adjustment for age, tumour stage and ECOG performance status, had a 73% (HR 0.27, 95% CI 0.10–0.75) reduction in risk of progression and 64% (HR 0.36, 95% CI 0.15–0.85) reduction in risk of death when compared to the HPV-negative patient [6]. Importantly, this was the first study to demonstrate tumour HPV status to be a strong and favourable prognostic biomarker in the context of a prospective analysis in a uniformly staged and treated patient population. However, because patients with HPV-positive tumours also have other favourable prognostic factors and the sample size of this study was small, tumour HPV status has yet to be demonstrated as an independent prognostic factor for oropharynx patients. Retrospective analyses are currently ongoing to determine whether similar survival differences can be observed in the context of large, randomised controlled clinical trials. In the first of these, presented as an abstract at ASCO in 2009, RTOG investigators found tumour HPV status to be an important and independent prognostic factor for oropharynx cancer and estimated the reduction in risk of death to be 50% after 4.5 years of follow-up [7].

The survival benefit for the HPV-positive patient reported in ECOG 2399 was observed in the context

of aggressive, multi-modality therapy. It is important to note, however, that *at this time it is unclear to what extent the survival benefit for the HPV-positive patient depends upon therapeutic choices*. The magnitude of the survival difference observed in the ECOG trial has similarly been observed in studies in which oropharyngeal cancer patients were treated with surgery with or without adjuvant radiation [8] or radiation with or without surgery [9]. In most of these studies, the 5-year overall survival for the HPV-positive patient is approximately 80–85% and for the HPV-negative patient between 30 and 35%. In fact, the data in total would suggest that *the survival benefit may be observed independent of the specific therapy administered, as long as it is within the current standard of care*. Therefore, patients with HPV-positive tumours may be unnecessarily exposed to therapy (induction chemotherapy followed by concurrent chemoradiation) which increases morbidity an estimated 400–500% compared to radiation therapy alone.

In addition to observational studies and clinical trials, the survival benefit observed for the HPV-positive patient may also be apparent at the population level, according to a recent analysis of over 47,000 incident cases of oral cancer reported to the Surveillance, Epidemiology, and End Results (SEER) programme of the National Cancer Institute, USA [10]. In the US, during the period from 1973 through to 2003, the incidence rate for cancers at sites etiologically related to HPV infection significantly increased, whereas significant declines in incidence were observed for oral cancers not etiologically related to HPV. In concert with this increase, from 1973–2003, significant improvements in absolute 2-year overall survivals were observed for patients treated with radiation therapy with local (~10.1 versus 5.3%) or regionally- (~23.1 versus 3.1% increase) advanced HPV-related cancers, but not for patients with HPV-unrelated cancers, respectively. Importantly, this study is consistent with the interpretation that recent improvements in the survival for patients with head and neck squamous cell carcinoma may, in part, be attributable to a shift in the underlying etiology of the disease and its inherent responsiveness to therapy.

The underlying biological reasons for the improved survival for the HPV-positive patient are not entirely clear, but appear to be multi-factorial: (1) Two prospective clinical trials have observed HPV-positive tumours to have a significantly improved response to chemotherapy when compared to HPV-negative tumours [6,11]; (2) Patients with HPV-positive tumours appear to have a lower risk of second primary cancers [8,12,13]; (3) Tumour HPV status inversely correlates with several poor prognostic biomarkers, such as a history of smoking, high epidermal growth factor receptor (EGFR) expression [11,14], inactivating p53 mutations [15,16], and nuclear survivin expression [16]. It is important to note, however, that some of these factors are so tightly correlated (e.g. p53 mutation and HPV-negative tumours) that it is difficult to discern whether or not each remains independently associated with survival after accounting for the other. For instance, one study has suggested that smoking was not a significant prognostic factor after accounting for HPV status [11], whereas another found HPV status had a minimal effect on survival outcomes among smokers, but smoking status had an important impact among HPV-positives. HPV-positive nonsmokers had the best outcome [12]. Similarly, tumour HPV status was suggested to account for the survival benefit observed among patients without p53-mutant tumours [8]. Correlative studies within large clinical trials conducted by the cooperative groups will be required to gain further insights into the molecular underpinnings of the survival difference, and will be important to the future potential of molecularly targeted therapies specific to the HPV-positive and HPV-negative patient.

In summary, at this time data support the conclusion that tumour HPV status is an important prognostic biomarker for head and neck cancers, particularly oropharyngeal cancer. Whether HPV status is associated with survival among the small proportion of non-oropharyngeal cancers (<5% or oral cavity or larynx cancers) that may be etiologically associated with HPV is unclear, and may be difficult to evaluate given the sample size that would be required. Nevertheless, it is clear that tumour HPV status should be incorporated, as a minimum, as a stratification factor in clinical trials including patients with oropharyngeal cancers. In the US, the Radiation Therapy Oncology Group has embraced this recommendation. In the ECOG, disease-specific trials for the HPV-positive versus HPV-negative patient are in development.

Conflict of interest statement

None declared.

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