HPV DNA as a Biomarker in Oropharyngeal Cancer: A Step in the Right Direction

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SUMMARY

Lack of prospectively planned follow-up and minimal characterization of the patient population studied complicate interpretation of circulating human papillomavirus (HPV) DNA as a prognostic biomarker for patients with HPV-associated oropharyngeal carcinoma treated with curative intent.

See related article by Berger et al., p. 4292

In this issue of *Clinical Cancer Research*, Berger and colleagues have provided us with a substantial experience with testing circulating tumor tissue modified viral (cTTMV) human papillomavirus (HPV) DNA following completion of treatment for oropharyngeal squamous cell carcinoma (OPSCC; ref. 1). The assay used is a derivative of the assay developed by Chera and colleagues (2, 3).

Their multianalyte digital droplet PCR (ddPCR) was designed to measure circulating cell free tumor tissue modified viral DNA (cTTMV DNA). The scientist in me wants to know how exactly the assay was developed, how it distinguishes tumor source circulating HPV DNA from non-tumor source HPV DNA and how different score cut-off points for positivity classification were selected for HPV subtype 16 versus the other serotypes. As a clinician, I take these test methodology details as a black box. The magic that happens inside that box is not as relevant to me as the outcome from that magic.

The outcome from that magic in the case of this experiment is noteworthy. More than 1,000 patients, after definitive treatment of HPV-related OPSCC, had over 1,300 cTTMV HPV DNA plasma assays performed as part of routine clinical care. 80 (7.4%) of those patients tested positive, 26 of whom had clinically active cancer documented prior to or concurrent with testing. 55 of the remaining 59 patients subsequently developed evidence of recurrent cancer, yielding a positive predictive value (PPV) of 95% for all positive patients and 93% for the patients without evidence of relapse at the time of the cTTMV HPV DNA assay. On the other hand, of the approximately 1,200 negative tests, 58 at the time of testing had clinically apparent disease yielding a point in time negative predictive value (NPV) of 95%. This atypical NPV endpoint is being reported because of very short follow-up and the nature of this project which was based upon data collected as part of routine medical care rather than a prospectively planned trial without long term follow-up.

Who were these patients? Outcomes for nonmetastatic patients vary substantially by T and N status. An HPV DNA biomarker might not perform uniformly across stage groupings. Biomarker outcomes for patients postsurgery could be different than for patients treated with radiation or chemoradiation or immunotherapy containing regimens. Recent data presented at the American Society of Clinical Oncology (ASCO) 2022 annual meeting by Sue Yom, MD, PhD from NRG HN 002, a randomized phase II chemoradiation study of low-risk HPV-associated patients with OPSCC, suggests a lower PPV for this TTMV HPV DNA assay when biobanked plasma drawn 2 to 4 weeks following chemoradiation was assayed (4, 5). S. Yom reported that in a subset of 128 patients for whom 2-year progression-free survival (PFS) and posttreatment plasma TTMV HPV DNA data were available, 3 of 8 (37%) with positive tests had evidence of progression at 2 years and 3 of 11 (27%) patients with progression within 2 years had positive posttreatment tests. The NPV for PFS in this trial was 112/120 (93%). Because we know so little from the Berger and colleagues report concerning patient tumor characteristics and treatments, it is not possible to explain the difference in the performance of the TTMV HPV DNA assay in the NRG HN 002 study versus the report by Berger and colleagues

To put the question of the value of plasma cTTMV HPV DNA monitoring in this setting into perspective, it is worth looking at present recommendations for post treatment evaluation. Following definitive chemoradiation treatment, National Comprehensive Cancer Network (NCCN) recommendations are for serial clinical examination, including fiberoptic exam as necessary, quarterly in the first year then less frequently over time. In addition, there is a recommendation for a single postsurgical imaging with either CT or MRI to establish a posttreatment baseline and in the case of definitive radiation-based treatment a single PET-CT approximately 3 months following treatment completion (6). These recommendations are based on small retrospective series demonstrating a high NPV for relapse for patients with radiologically negative imaging, especially PET-CT in the case of postradiation patients (7, 8). In the case of PET-CT scans for oropharynx cancer, the 3-month posttreatment PET-CT is most useful in terms of NPV which meta-analysis suggests exceeds 96% (7). Positive predictive value has been estimated to be only 53%. There are no substantial data to support subsequent prognostic biomarker use of any kind, including PET-CT (9).

For patients with oropharyngeal carcinoma following definitive treatment, the surveillance landscape is largely devoid of useful data driven advice beyond these single posttreatment scans. The NCCN recommendations for an anatomically adjacent disease, Epstein-Barr virus (EBV)-driven nasopharyngeal cancer (NPC), include consideration of plasma EBV DNA monitoring with a lower recommendation rating of 2b, based on numerous reports demonstrating that circulating EBV DNA postdefinitive radiation-based treatment strongly correlates with relapse. Detection of circulating tumor EBV DNA in patients followed long term is also known to correlate with subsequent relapse. Prospective evaluations of uniformly treated patients with NPC with a standardized circulating EBV DNA assay have not been of

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sufficient robustness to merit a high level of confidence concerning the clinical utility of EBV testing in patients with NPC (10–12).

Into this landscape comes circulating tumor HPV DNA assays. Are the data presented in this paper by Berger and colleagues good enough to propose wide adoption of cTTMV HPV DNA as a biomarker for prognosis in these patients or should we ask that more studies be done prior to the routine adoption of this assay? Given the preliminary report from the NRG HN 002 associated data, how comfortable can one be with the applicability of the high PPV cited in this report to the next patient one treats? Is it good enough to have an assay with an extraordinarily high PPV but questionable NPV from an ad hoc but very large dataset collected from routine practice? How closely do the patients assayed in this study resemble patients for whom this assay might be recommended? Can one assume that there was no unrecognized bias in selection of patients studied here that might explain the extraordinarily high PPV for cTTMV HPV DNA testing described here? Should one expect higher level of evidence from prospective randomized studies demonstrating evidence for a change in the overall survival or disease-free survival rather than merely prognostic value?

No other biomarker for relapse or persistent disease, including CT, PET CT, physical examination, or EBV DNA testing in nasopharynx cancer has risen to the level of evidence of benefit these questions propose. The anecdotes presented by Berger and colleagues suggesting that early detection of relapse or persistence through cTTMV HPV DNA monitoring may offer the hope of curative salvage, while intriguing, certainly cannot be the basis for sweeping recommendations for adoption of posttreatment surveillance with this tool. However, one should not ignore the potential patient benefit of early relapse prediction even in the absence of effective salvage treatment. For centuries the value of prognostic accuracy in all of medicine has been valued, even when physicians have no way to alter prognosis. Patients may find great benefit from knowing more accurately what is to come, and when, despite no ability to alter nature's course.

I am left to conclude that while it would be impractical and naive to ask that this cTTMV HPV DNA assay not be used in the posttreatment surveillance setting at all, widespread adoption will impair the ability both to define more accurately the potential benefit and to optimize its use. I fear that physicians will reassure patients in this setting that the negative TTMV HPV DNA assay implies they are in a particularly low-risk group. Yet the single point in time NPV of 95% from Berger and the 2-year PFS NPV of 93% from NRG HN 002 look remarkably like the overall 2-year PFS of 90% described for chemoradiation patients in NRG HN 002 (4). Similarly, until the extraordinarily high PPV of the Berger and colleagues study are reconciled with the modest PPV from the NRG HN002 experience, I cannot endorse use of the assay to reliably detect relapse. I can only hope and beg that controlled studies will be conducted for cTTMV HPV DNA assays and all such biomarkers so that we can optimize the patient benefit derived from their use.

Patients with HPV-associated locoregional OPSCC are fortunate in that the vast majority are cured using conventional treatment. Reported cure rates in these patients typically exceeds 80%. The Naveris list price for the TTMV HPV DNA assay is $1,800. Serial sampling is already occurring in more than 20% of these patients according to the Berger and colleagues report. Based upon the data presented, the vast majority of these tests will be neither actionable nor offer substantially different prognostication. Further evaluation of the clinical utility of HPV DNA testing should therefore include a robust cost benefit analysis taking into account all costs associated with a post treatment monitoring strategy.

Might such an assay be used in early detection for a high-risk population? While pretreatment circulating tumor EBV DNA levels have been shown to be an independent prognostic factor for patients with NPC and will probably be incorporated into future staging criteria for NPC, circulating tumor HPV DNA levels in patients with treatment-naïve OPSCC have not as reliably correlated with prognosis (2). It is also possible that circulating tumor HPV DNA assays will find a place in response assessment during treatment with subsequent treatment modification in both the curative and the recurrent metastatic settings. Controlled clinical trials with embedded biomarkers will be necessary to optimize the utility of circulating tumor HPV DNA assays.

Author's Disclosures

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