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Disclosure

SS has acted in a consulting or advisory role to Amgen, Bayer, BMS, Daiichi-Sankyo, Ignyta, Lilly, Merck, Merus, Novartis, Roche, and Sanofi. AS-B has acted in a consulting or advisory role to Amgen, Bayer, Lilly, and Sanofi. All remaining authors have declared no conflicts of interest.

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Prognostic utility of HPV specific testing in addition to p16 immunohistochemistry in oropharyngeal squamous cell carcinoma

We read with interest the paper by Nauta et al. [1] since it relates to our own experience. The authors described a sub-cohort of oropharyngeal squamous cell carcinomas (OpSCCs) that was p16 positive (+) but HPV DNA negative (−) demonstrating poorer overall survival (OS) compared with p16+/HPVDNA+ individuals. We too have identified p16+/HPVDNA− cases within a UK population, a country with a higher prevalence of p16+ OpSCC than the Netherlands.

In our study, 238 OpSCC specimens from a single centre were assessed using p16 immunohistochemistry (CINtec®, Ventana Medical Systems). A total of 153 cases (64.3%) were p16+ and were subsequently tested for high-risk (HR) HPV DNA using in-situ hybridisation (ISH, Ventana Medical Systems). Of the p16+ cases, 127 (83.0%) were HRHPV DNAISH+ whilst 26 (17.0%) were HRHPV DNAISH−. The p16+/HPVDNA− rate in our cohort was higher than that reported by Nauta et al. (17.0% versus 12.4%), which may be explained by differences in sensitivity and specificity between DNAISH and PCR [2].

Similar to Nauta et al., our p16+/HPVDNA− cases demonstrated improved OS compared with p16− individuals but showed poorer survival than p16+/HPVDNA+ patients ($P < 0.001$; Figure 1A). Our p16+/HPVDNA− patients demonstrated better OS compared with the Dutch cohort and this too may be explained by the suboptimal sensitivity of DNAISH [2].

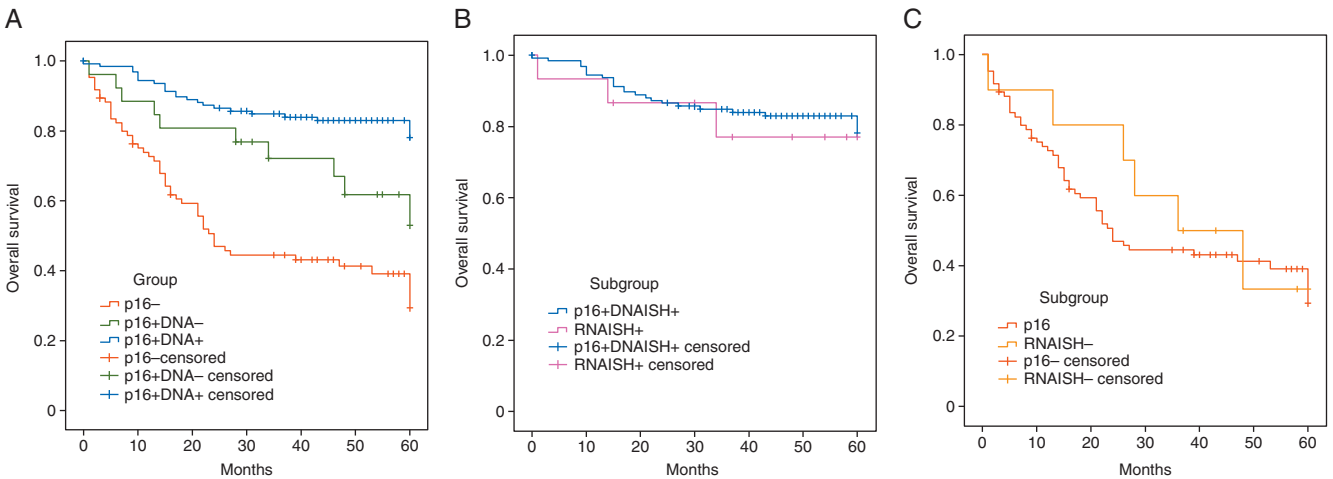

Figure 1. (A) Kaplan–Meier curve for overall survival according to p16+/DNAISH+ (blue line), p16+/DNAISH− (green line), p16− (red line) status (Log rank test; χ^2=48.83; df=2; $P < 0.001$). Significant difference in 5-year overall survival was seen between p16+/DNAISH− (green line) and p16− (red line) cases ($P = 0.023$), as well as between p16+/DNAISH− (green line) and p16+/DNAISH+ (blue line) cases ($P = 0.022$). (B) Kaplan–Meier curve for overall survival according to p16+/DNAISH+ (blue line) and p16+/DNAISH-/RNAISH+ (pink line) status (Log rank test; χ^2=0.12; df=1; $P = 0.727$). (C) Kaplan–Meier curve for overall survival according to p16+/DNAISH−/RNAISH− (orange line) and p16− (red line) status (Log rank test; χ^2=0.29; df=1; $P = 0.626$).

Since p16+/HPVDNAISH− cases could be due to either false positive p16 or false negative DNAISH, we used mRNAISH (RNAScope, ACDBio) as a third-tier test to resolve HPV status in p16+/HPVDNA− cases. This enabled us to further classify 15 (57.7%) and 11 (42.3%) cases as positive and negative for HRHPV, respectively. Interestingly, the OS of p16+/HPVDNAISH-/HPVRNAISH+ was similar to that of p16+/HPVDNAISH+ (Figure 1B), likely reflecting the greater sensitivity of mRNAISH [3]. Conversely, there was no significant difference in OS between p16+/HPVDNAISH−/HPVRNAISH− and p16− OpSCCs ($P = 0.626$, Figure 1C). Our data therefore support the findings of Nauta et al. in demonstrating poorer survival outcomes of p16+/HPVDNA− compared with p16+/HPVDNA+ OpSCC. We agree that it is important 'to perform additional HPV DNA testing for predicting prognosis and when considering treatment de-intensification' [1].

Several authors have recently detailed the performance and utility of various laboratory HPV testing options in OpSCC [3, 4]. In this context, it is important to note that inaccurate assessment of HPV status presents a hazard to patients enrolled in de-intensification trials by inappropriately assigning individuals to dose-reduction arms. In addition to exposing patients to sub-therapeutic regimes, the lack of specificity of p16 indicates that results of such de-intensification trials need to be interpreted with caution. To avoid such complications, we recommend a tiered algorithm utilising p16 immunohistochemistry, HR-HPV DNAISH and HR-HPV mRNAISH where the last provides an alternative to PCR in p16+/DNAISH− cases.

It may be tempting to recommend mRNAISH as a single assay for HPV classification in OpSCCs, but a tiered algorithm with two or more strata almost always demonstrates greater utility in avoiding inaccurate results. Furthermore, the cost implications and lack of widespread availability restricts the routine use of mRNAISH as the second-tier test in p16+ OpSCCs [5]. We therefore suggest that mRNAISH be reserved as a third-tier test for OpSCCs that are p16+/DNAISH−. Patients with p16+ tumours that show negativity with both DNAISH and mRNAISH could represent a separate sub-group with a different prognosis altogether, and as such should be considered for exclusion from de-intensification trials.

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Heterogeneity of *EGFR*-mutant clones and PD-L1 highly expressing clones affects treatment efficacy of EGFR-TKI and PD-1 inhibitor

Current clinical trials have suggested poor efficacies of programmed death-1 (PD-1) blockade therapies for non-small-cell lung cancer (NSCLC) harboring epidermal growth factor receptor (*EGFR*) mutations [1]. However, there is controversy about the use of PD-L1 expression as a surrogate marker for response to PD-1 blockade therapy as a biomarker [2]. Here, we show an NSCLC case with PD-L1 highly expressing *EGFR*-mutant NSCLC who responded dramatically to PD-1 blockade therapy but not to an EGFR-TKI due to intratumor heterogeneity.

A 62-year-old Asian woman presented at our hospital complaining of dry cough and gait disturbance due to right hip pain. She was a current smoker with 62 pack-years and had a history of hypertension and osteoarthritis of the right hip. She had no previous malignancies in the past and no family history of cancer. A computed tomography (CT) scan revealed a 65 mm mass in the right ilium and a 16 mm nodule in the lung. CT-guided biopsy showed the mass of the right ilium was metastasis from lung adenocarcinoma with *EGFR* exon 19 deletion (Ex.19 del) detected by the PNA-LNA PCR clamp method. PD-L1 tumor proportion score (TPS) was 90%. Erlotinib and radiotherapy to the right ilium were started. However, follow-up CT carried out 2 months later detected multiple new metastases. CT-guided biopsy of the right chest wall metastasis was carried out. Biomarker screening detected no *EGFR* mutations in the tumor and PD-L1 staining showed TPS 95%. Pembrolizumab was administered as the second-line therapy. During the first course, her right hip pain dramatically improved and CT after three cycles of pembrolizumab showed complete disappearance of primary lesion and multiple metastases. Immunofluorescent analysis of both right ilium and chest wall