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High-sensitivity human papilloma virus genotyping reveals near universal positivity in anal squamous cell carcinoma: Different implications for vaccine prevention and prognosis

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Abstract ***Background:*** Characterisation of human papilloma virus (HPV) infection in anal squamous cell carcinoma (ASCC) may have dual importance: first, aetiological; second, prognostic, informing outcome after chemo-radiotherapy (CRT). We undertook HPV genotyping, and allelic characterisations, to evaluate the aetiological role of HPV while simultaneously evaluating the impact of HPV genotyping on relapse-free (RFS) and overall survival (OS).
Method: Dual-primer HPV genotyping (subtypes 6, 11, 16, 18, 31, 33, 45, 52, 58) and DNA sequencing of HPV 16 positive tumours were analysed in 151 consecutively referred ASCCs, previously characterised by immunohistochemistry for p16 expression. In 110 patients treated with CRT, factors influencing RFS and OS were evaluated using univariate and multivariate models.
Results: HPV positivity was observed in 95%. HPV 16 accounted for 89%; of these, 64% harboured the T350G E6 variant. HPV 16 positivity was significantly correlated with improved 5-year RFS (62% versus 40%; $p = 0.027$) and OS (59% versus 38%; $p = 0.019$). p16 expression was also significantly correlated with improved 5-year RFS (positive versus negative: 65% versus 16%; $p < 0.0001$) and OS (63% versus 13%; $p < 0.0001$). In multivariable

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models that included HPV 16 status, p16 status, sex, and age, p16 expression remained an independent prognostic factor for RFS ($p < 0.0001$) and OS ($p = 0.002$).

Conclusion: In ASCC, near-universal HPV detection rates were demonstrated, higher than generally reported in the literature, and supporting the development of multivalent HPV vaccinations for prevention. By contrast, p16 negatively, but not HPV 16 genotype, is an independent adverse prognosticator after chemo-radiotherapy in patients with ASCC.

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1. Introduction

Anal squamous cell carcinoma (ASCC) is a rare malignancy with annual incidences ranging from 1.0 to 2.5 per 100,000 population in many western countries [1]. In several countries, incidence rates have increased two-to-three fold in the past three decades. Epidemiological and experimental evidence indicates that human papillomavirus (HPV) infection is a key aetiological factor for ASCC [2], but the overall HPV detection rate is dependent upon the number of subtypes screened and the sensitivity of assays employed. In 2009, a meta-analysis of 29 studies [3], using mainly historical detection assays, reported an estimate for HPV positivity of 84.3%. Recently published data suggest that the overall HPV positivity rate might be as high as 95% [4,5].

There is general consensus that HPV 16 is the most prevalent HPV subtype in ASCC, being present in up to 90% of tumours, with HPV 18 prevalence being considerably less. This contrasts with cervical carcinoma, where the HPV 16 and 18 detection rates range from 55% to 70%, and 15% to 20%, respectively [6]. HPV-associated cancers are potentially preventable through population-level HPV vaccination. Clinically available vaccines include bivalent (HPV 16, 18) and quadrivalent (HPV 6, 11, 16, 18) agents. In young women, the effectiveness of these vaccines to protect against the subsequent development of precursor cervical intraepithelial neoplasia has been confirmed in randomised trials [7–9]. Vaccines with broader coverage are under development [10]. To better inform the potential effectiveness of these new multivalent vaccines as cancer prevention strategies, there is a need to better understand tumour-specific patterns of HPV infection.

The mainstay of initial treatment for ASCC is chemo-radiotherapy (CRT). This approach generally achieves good local control and avoidance of radical surgery [11,12]; but early and late toxicities remain considerable [13,14]. Tumour-specific HPV detection is a potential prognostic biomarker after CRT and may select for stratified approaches to treatment. After HPV genomic integration into host cells, two early structural genes, E6 and E7, known tumour oncogenes, contribute to genetic instability through inactivation of p53 and the retinoblastoma protein (pRb), respectively (more details, ESM text p1). Differences in the transformation activity and progression of HPV may be attributed to allelic variations of E regions [15] - for example, L83V (corresponding to European variant T350G), may be associated with disease progression [16]. pRb is a negative regulator of the cyclin-dependent kinase inhibitor $p16^{INK4A}$ (p16), such that expression of p16 is a surrogate biomarker of HPV infection [17]. HPV positivity and/or p16 expression in oropharyngeal cancers are associated with a distinct phenotype with good prognosis and complete response to CRT [18–20]. Similar patterns are noted for cervical carcinoma [21]. A number of studies are emerging in which HPV positivity and/or p16 expression are prognostic for improved survival in patients with ASCC treated by CRT [17,22–24].

Given the dual (aetiology and prognosis) importance of characterisation of HPV infection in ASCC, here, we undertook HPV genotyping, and allelic characterisations, to better inform aetiological pathways, while simultaneously evaluating the impact of HPV genotyping as compared with p16 expression on relapse-free (RFS) and overall survival (OS). To enhance the sensitivity of our assay, we used a dual-primer HPV genotype assay [25]; to interpret our results in line with multi-valent vaccine development, we genotyped for nine low- and high-risk oncogenic HPV subtypes.

2. Methods

2.1. Patients and treatment

The study was based on pre-treatment biopsies collected from patients with ASCC presenting consecutively at the Sussex Cancer Centre, Brighton, and the Kent Oncology Centre, Maidstone, United Kingdom (UK) (2004 and 2009). For patients with non-metastatic disease, standard care was CRT (50.4 Gy in 28 fractions plus concurrent 5-fluorouracil and mitomycin) using the UK National Anal Cancer Trial (ACT II) protocol [26]. Patient characteristics, HIV status, tumour characteristics, treatment details, relapse, follow-up and vital status were obtained from clinical case notes. This work was granted ethical approval by the relevant ethics committee (11/LO/1032).

2.2. Tissue and DNA extraction

Formalin-fixed paraffin-embedded (FFPE) tumour blocks were obtained under anonymous study numbers.

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