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Clinical implications of human papillomavirus genotype in cervical adeno-adenosquamous carcinoma

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Abstract ***Background:*** Our aims were to evaluate the genotype distribution of human papillomavirus (HPV) and the correlation between HPV parameters and clinicopathological/treatment variables with prognosis in cervical adeno-adenosquamous carcinoma (AD/ASC).
Patients and methods: Consecutive patients who received primary treatment for cervical AD/ASC International Federation of Gynecology and Obstetrics (FIGO) stages I–IV between 1993 and 2008 were retrospectively reviewed. Prognostic models were constructed and followed by internal validation with bootstrap resampling.
Results: A total of 456 AD/ASC patients were eligible for HPV genotyping, while 452 were eligible for survival analysis. HPV18 was detected in 51.5% and HPV16 in 36.2% of the samples. Age >50 years old, FIGO stages III–IV and HPV16-negativity were significantly related to cancer relapse, and age >50, FIGO stages III–IV, HPV16-negativity and HPV58-positivity were significant predictors for cancer-specific survival (CSS) by multivariate analyses. HPV16-positivity was also significantly associated with good prognosis in those receiving primary

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radiotherapy or concurrent chemoradiation (RT/CCRT) (CSS: hazard ratio 0.41, 95% confidence interval 0.21–0.78). Patients with FIGO stages I–II and HPV16-negative AD/ASC treated with primary RH-PLND had significantly better CSS ($p < 0.0001$) than those treated with RT/CCRT.

Conclusions: Age >50 years old, FIGO stages III–IV and HPV16-negativity were significant poor prognostic factors in cervical AD/ASC. Patients with HPV16-negative tumour might better be treated with primary surgery (e.g. radical hysterectomy for stages I–II and pelvic exenteration for stage IVA). Those with unresectable HPV16-negative tumour (stage IIIB) should undergo CCRT in combination with novel drugs. The inferences of a single-institutional retrospective study require prospective studies to confirm.

1. Introduction

Cervical carcinoma is the third most common cancer among women worldwide.[1] Thanks to the Pap smear screening, the overall incidence rates of invasive cervical carcinoma are decreasing, while trends showing an increasing ratio of glandular cancers have been noted in the United States (US) and in Taiwan.[2,3] A study of cervical adenocarcinoma (AD) incidence rates in Europe found a decline in period-specific rates in the United Kingdom, Denmark and Sweden with a general increase in other countries.[4]

A meta-analysis of eight pooled case-control studies found that the adjusted odds ratio for cervical AD or adenosquamous carcinoma (ASC) in human papillomavirus (HPV)-positive women compared with HPV-negative was 81.3 (95% confidence interval = 42.0–157.1).[5] Although AD/ASC shares many common risk factors including HPV infections with squamous carcinoma (SC) except smoking,[6] tumour gene expression profile and biology of different histologic types seems different in some ways.[7,8] Whether AD/ASC should be treated differently from SC has been controversial.[8,9] Previous studies indicated that AD/ASC histology and metastasis to lymph nodes were risk factors for poor outcome regardless of primary irradiation or surgery.[8,10]

HPV18 or alpha-7 species were over-presented in AD/ASC rather than SC in previous studies.[11,12] HPV18 has also been confirmed as a significant prognostic factor in invasive cervical cancers (SC and AD/ASC together) after adjusting for confounding factors.[13–16] However, AD/ASC comprised 10–24.1% of all cervical cancers[8,9]; whether HPV genotype independently impacts on outcome was not clear.

The aims of this study were to evaluate the distribution of HPV genotype and the correlation between HPV parameters and clinicopathological/treatment variables and prognostic factors including HPV variables in cervical AD/ASC patients treated between 1993 and 2008. Prognostic modelling was constructed and followed by internal validation.

2. Patients and methods

2.1. Study population

Consecutive patients who underwent primary definitive surgery or radiotherapy (RT) for invasive cervical carcinoma of FIGO stages I–IV between 1993 and 2008 at Chang Gung Memorial Hospital were retrospectively reviewed. Formalin-fixed paraffin-embedded tissue specimens were used for DNA analysis. Eliminating those who had a wrong diagnosis or incomplete medical records, with missing paraffin blocks, and with inadequate DNA quality, the remaining patients were eligible for the HPV genotype study.[13,14,17] Results of the 1993–2000 dataset[13,14,17] we partly reported previously. Data for HPV genotype and survival/recurrence in SC ($n = 926$) receiving RT or concurrent chemoradiation (CCRT)[14] and SC undergoing primary surgery ($n = 889$)[13] were retrieved from the previous database for comparisons. Survival rates and recurrences were updated to 8th March 2012.

2.2. HPV genotyping

The procedures of DNA extraction and polymerase chain reaction (PCR) have been detailed previously.[13,14,17,18] Briefly, SPF1/GP6+ PCR were performed for 40 cycles. E6 Type-specific PCR was performed for 50 cycles. The primer sequences and procedures of type-specific PCR were detailed in previous reports.[13,14,17–19] Routine precaution procedures were applied to avoid carrying-over or contamination.[13,14,17,18]

Fifteen microlitres of the resultant amplimers was then hybridized with an HPV Blot (King Car, I-Lan, Taiwan) membrane, in which 38 types of HPV (6, 11, 16, 18, 26, 31, 32, 33, 35, 37, 39, 42, 43, 44, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 62, 66, 67, 68, 69, 70, 71 [CP8061], 72, 74, 81 [CP8304], 82 [MM4], 83 [MM7], 84 [MM8], L1AE5) could be detected, as previously described.[13,14,17–19]