REVIEW

Recent data about the role of human papillomavirus (HPV) in oncogenesis of head and neck cancer

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Abstract

Human papillomavirus (HPV) is a small circular DNA-virus and the high-risk types 16, 18 is implicated in oncogenesis of head and neck cancer – especially oropharynx (tonsil and base of tongue), poorly differentiated (the basaloid type), locoregional advanced stage, poorly differentiated, at the younger male, non-smokers, non-drinkers, sexual behaviors. The prognostic is favorable of human papillomavirus tumor status for patients with oropharynx squamous cell carcinoma treated with radiotherapy (accelerated fractionation without total dose reduction). The impact of HPV-vaccination (ACIP 2007) decreasing the incidence of oropharyngeal cancer, but that patients HPV-positive, have good prognostic in generally (two-year overall survival: 95%, two-year progression-free survival: 88%), therefore HPV-vaccination in routine practice it is controversy.

***Keywords*:** human papillomavirus, head and neck cancer, prognosis, treatment.

Introduction

Almost 650 000 patients worldwide are diagnosed with head and neck cancer each year and 350 000 patients die from this disease. The head and neck squamous cell carcinoma risk factors were tobacco and alcohol use (account for disease pathogenesis in about 80% of the cases in patients of average age 50–60-year-old).

Human papillomavirus accepted etiologic agent for cervical carcinoma and first reported association with head and neck cancer in 1985. However, in contrast to cervical cancer, establishing the link between high-risk HPV-infection and the development of head and neck cancer is far more difficult [1, 2].

Numerous lines of epidemiologic and molecular evidence suggest that high-risk human papillomaviruses, especially type 16, 18 are etiologically related to a subset of head and neck cancer, especially oropharyngeal squamous cell cancers (Table 1) [3, 4].

The data of National Program of Cancer Registries (NPCR) and Surveillance, Epidemiology and End Results (SEER) program included information from 38 States and the District of Columbia, covering 1998–2003, demonstrated that head and neck cancers attributable HPV 16, 18 are tonsil and base of tongue at the male with 60–69-year-old [6–10].

In addition, the data included information from 37 EU Cancer Registries showed that incidence of head and neck cancer with HPV 16, 18 was similarly: tonsil and base of tongue [6].

Head and neck cancer are important mortality, incidence and prevalence in worldwide and also in Romania, and for this fact, the authors considered necessary to make a study for epidemiologic and genetic human papillomavirus detection is establishing the link between high-risk HPV-infection and the development of poor head and neck cancer especially oropharynx and larynx at the older man.

Table 1 – ***The link between high-risk HPV-infection 16, 18, 6, 11 and the development of head and neck cancer or other type cancer [1, 2]***

HPV-types	Estimated attributable [%]
HPV 16, 18	
Cervical cancer	70%
High grade cervical abnormalities	50%
Low grade cervical abnormalities	30%
Anal cancer	70%
Vulvar / vaginal / penile cancers	40%
Head and neck cancers	10%
HPV 6, 11	
Low grade cervical abnormalities	10%
Genital warts	90%
Recurrent respiratory papillomatosis (RRP)	90%

Pathogenesis

The rationale for epidemiologic and genetic human papillomavirus detection is establishing the link between high-risk HPV-infection and the development of head and neck cancer and the prognostic significance of human papillomavirus tumor status (the response of treatment, surveillance for recurrence and surveillance for second primary tumor development).

HPV–DNA presence in tumors *per se* does not prove causal association. This is possible when

molecular techniques show that the virus is required for malignant of tumor cells [5, 11, 13–15, 20–25].

In cervical cancer, caused by infection with high-risk HPV-types, discovered the major HPV-oncogenes E6 and E7 expressed in cervical cancer cells, and these genes are responsible for oncogenesis in cervical cancer (Table 2).

Table 2 – ***Major human papillomavirus oncogenes [5]***

E1	Viral replication maintains episome.
E2	Transcriptional regulation co-factor for viral replication.
E4	Disrupts cytokeratins.
E5	Interacts with growth factor receptors.
E6	Transforming protein; p53 degradation.
E7	Transforming protein; Rb binding.
L1, L2	Coding for major and minor capsid proteins.

Continued expression of E6 and E7 is required to maintain the proliferative state of cervical cancer cells.

E2 protein represses transcription of the E6 and E7 genes. This results in reactivation of the p53 and Rb tumor suppressor pathways and cell growth arrest.

The grow-arrested cells rapidly become senescent.

Antisense-mediated repression of HPV-oncogene expression in cervical cancer cell lines typically results in several fold inhibition of proliferation (Figure 1).

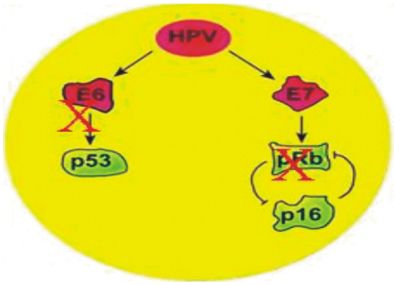

Figure 1 – ***Major human papillomavirus oncogenes: two main viral proteins (E6, E7) affect cellular p53 and pRb pathways [5].***

The effect of repression of E6 and E7 oncogenes on the transformed phenotype of HPV+ head and neck cancer cell lines has not been determined. To be necessary determine the consequences of removing E6 and E7 on the malignant phenotype, the sequence of biochemical events induced by repression of E6 and E7 gene expression and the changes of cellular transcriptional profile after E6/E7 silencing in HPV 16+ oropharyngeal cancer cell lines [5, 11, 13–15, 23, 24].

The genetic technique detected this cellular events infection of 93VU147T bearing integrated HPV16DNA oropharyngeal cancer cell lines [92VU040T HPV negative] with retrovirus vectors encoding for short hairpin RNAs targeting the E6 or E7 genes [5, 11, 13–15, 23, 24].

The integrated HPV16 genome is detection with *in situ* hybridization FISH, and RT–PCR detection of E6/E7 transcriptional profile before and after E6/E7 silencing.

Continued expression of E6 and E7 is required to maintain the proliferative state of HPV-associated oropharyngeal squamous cancer cells. Repression of E6 and E7 oncogenes after infection with shRNA results in reactivation of the p53 and Rb tumor suppressor pathways and in apoptosis [5, 11, 13–15, 23, 24].

Therapeutical implications

The link between high-risk HPV-infection and the development of subtype head and neck cancer and the prognostic significance of human papillomavirus tumor status was studies in a prospective multicenter phase II clinical trial – Eastern Cooperative Oncology Group (Phase III trial-not feasible) (Figure 2) [12, 13, 17–19, 22].

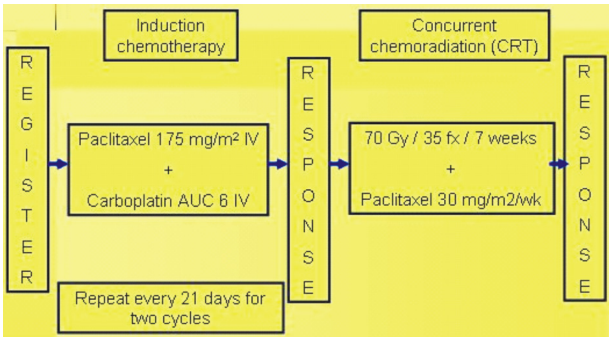

Figure 2 – ***Multicentric phase II study – ECOG 2399 (Eastern Cooperative Oncology Group) [12].***

The study included patients with advanced head and neck cancer treated with induction chemotherapy (two cycles: Paclitaxel 175 mg/mp i.v. + Carboplatin AUC6 i.v.) followed concurrent chemoradiation (Paclitaxel 30 mg/mp/weekly, 70 Gy/35 fr/7 weeks) for the patients with response after induction therapy. In this study, the authors intended to find HPV 16, 31, 33, 35 with *in situ* hybridization FISH or DNA-extraction with PCR and papillomavirus was detected at younger man, non-smokers, non-drinkers, sexual behaviors and poorly differentiated (basaloid) histological type, advanced locoregional study (Table 3) [12, 13, 17–19, 22].

Table 3 – ***Multicenter phase II clinical trial ECOG 2399 (Eastern Cooperative Oncology Group) [12]***

	HPV-positive	HPV-negative
Oropharynx	38	24
Larynx	0	34
Total	38 (40%)	58 (60%)

Multivariate prognostic analyze demonstrated the etiopathogenetic role of HPV in poor head and neck carcinoma oropharynx (palatine and lingual tonsils), poorly differentiated (basaloid), especially at younger man, nonsmokers, nondrinkers, sexual behaviors and advanced locoregional disease. The prognostic at the positive HPV-patients was statistical significant higher-response rate (especially after induction chemotherapy (p=0.01) and after all the treatment (p=0.07), two-year overall survival (p=0.004) and two-year progression free survival (p=0.05) [12, 13, 17–19, 22].

Because this sensitivity to chemotherapy and radiotherapy for oropharyngeal patients HPV-positive the question is: non-oropharyngeal cancer (especially HPV-negative) should be better treated with non-RT (i.e., surgery)?

However, only prognostic factor with statistical significant for the therapeutic response, overall survival and progression-free survival is altered fractionated radiotherapy.

The radiotherapy is only therapy with increased local control, and many phase II trial studied the effect of altered fractionated radiotherapy compared conventional radiotherapy (hyperfractionation accelerated fractionation without/with total dose reduction) and the accelerated fractionation without total dose reduction is statistical significantly for overall survival (p=0.02) (Table 4) [19, 23–25].

Table 4 – ***Prognostic value of radiotherapy [19]***

	Hyperfractionation	Accelerated fractionation without total dose reduction	Accelerated fractionation with total dose reduction	All three groups	*p*
Overall survival	0.78 (0.69–0.89)	0.97 (0.89–1.05)	0.94 (0.84–1.05)	0.92 (0.86–0.97)	0.02
Death from cancer	0.78 (0.68–0.90)	0.91 (0.83–1.00)	0.93 (0.83–1.05)	0.88 (0.83–0.94)	0.13
Non-cancer death	0.79 (0.57–1.10)	1.19 (1.00–1.42)	0.93 (0.74–1.29)	1.06 (0.93–1.22)	0.08
Locoregional control	0.76 (0.66–0.89)	0.79 (0.72–0.87)	0.90 (0.80–1.02)	0.82 (0.77–0.88)	0.15
Local control	0.75 (0.63–0.89)	0.74 (0.67–0.83)	0.83 (0.71–0.96)	0.77 (0.71–0.96)	0.50
Regional control (nodal)	0.83 (0.66–1.03)	0.90 (0.77–1.04)	0.87 (0.72–1.06)	0.87 (0.79–0.97)	0.83
Metastatic control	1.09 (0.76–1.58)	0.93 (0.74–1.19)	0.95 (0.68–1.32)	0.97 (0.82–1.15)	0.77

In the future, the open question for head and neck SCC–HPV positivity, which will be the impact of HPV-vaccination (ACIP 2007) on males' decreasing oropharyngeal cancer?

However, the patients HPV-positive, have good prognostic in generally (two-year overall survival: 95%, two-year progression-free survival: 88%), therefore HPV-testing in routine practice it is controversy.

HPV 16, 18 associated HNSCC-oropharynx, palatine and lingual tonsils, locoregional advanced, poorly differentiated (basaloid), at males' non-smokers, non-drinkers, younger age, sexual behaviors.

The oropharyngeal patients' cancer HPV-positive treated with accelerated fractionation radiotherapy without total dose reduction have good prognostic (response rate, overall survival and progression-free survival).

Anti-HPV strategies may be effective in the treatment of HPV-associated head and neck cancers because over the last several decades, mortality rates have not changed significantly.

Further analysis-quantifying stage for HPV+ *vs.* HPV- cancers and examine mortality data with respect to HPV+ *vs.* HPV- cancers.

It is necessary to conduct population-based baseline and periodic HPV-typing of head and neck cancers to assess the impact of the HPV-vaccine.

An operational Cancer Registry is necessity to provide in formation and strategies needed in large-scale cancer control into certain population.

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