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M. K. Ibragimova' , M. M. Tsyganov' , I. V. Karabut' , L. A. Kolomiets' , E. L. Choynzonov' , and N. V. Litviakov'

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Disease-free and Overall Survival of Patients Diagnosed with HPV-associated or HPV-negative Cervical Cancer

M. K. Ibragimova[1, 2, a)], M. M. Tsyganov[1, 2, b)], I. V. Karabut[1, c)], L. A. Kolomiets[1, d)], E. L.Choynzonov[1, e)], N. V. Litviakov[1, 2, f)]

[1]*Tomsk Cancer Research Institute, 5, Kooperativny Street, 634050, Tomsk, Russia*
[2]*National Research Tomsk State University, Lenina Avenue, 36, 634050, Tomsk, Russia*

[a)]Corresponding author: Imk1805@yandex.ru
[b)]tsyganovMM@yandex.ru
[c)]airikarabut@mail.ru
[d)]kolomietsla@oncology.tomsk.ru
[e)]nii@oncology.tomsk.ru
[f)]nvlitv72@yandex.ru

Abstract. The real-time PCR method is used to study scrapings of cervical epithelium and outer portion of the cervix in 116 patients aged 24–79 years with stage I–IV primary cervical cancer. The comprehensive survey included colposcopy, cytological and histological analysis, detection and genotyping of high-risk human papillomavirus. In 84 patients (72.4%) the presence of human papillomavirus (HPV) of high carcinogenic risk (HCR) is found, in 32 patients (27.6%) the presence of the virus has not been inspected in the tumor. A significant decrease in the survival rate as well as the prevalence of the worst prognosis for patients with HPV-negative cervical cancer are shown.

INTRODUCTION

Nowadays, human papillomavirus (HPV) is considered to be the main causative agent of cervical cancer progression [2]. According to various studies, up to 80–90% of patients diagnosed with cervical cancer are also carriers of high-risk HPV [15], thus up to 20% of cervical tumor DNA does not contain the virus.

This gives reason to suggest that some tumors can occur without the virus (or the virus can be eliminated during oncogenesis), i.e. such tumors are HPV-negative. Some researchers claim that such cervical cancer subtype may be encountered only due to lab test errors [1].

There is, however, another view of the phenomenon. Along with HPV-associated cervical cancer, there is HPV-negative tumors, which belong to a more aggressive tumor class and whose oncogenesis essentially differs from that of HPV-associated tumors [14].

The study of head and neck tumors shows that HPV-negative ones have higher relapse and death rates than HPV+ tumors [3, 5, 8], the same statement is applicable for patients diagnosed with anus tumors. A group of HPV16+ patients demonstrated a high 4-year relapse-free survival, compared to HPV16- patients (63.1% to 15.6%, $p<0,001$), as well as the overall survival (84.6% to 39.8 %, $p=0,008$) [18].

Due to an insufficient number of studies dedicated to HPV- cervical tumor oncogenesis mechanisms, their response to anticancer therapy, and peculiarities of such patients' relapse and survival, this type of research is considered to be important today.

The aim is to evaluate relapse-free and overall survival for HPV+ and HPV- patients diagnosed with primary cervical cancer.

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MATERIALS AND METHODS

The research included 116 residents of the Tomsk Region aged from 24 to 79 years diagnosed with stage I–IV primary cervical cancer examined and treated in the Tomsk Cancer Research Institute. The diagnosis was histologically verified; tumors were defined according to the FIGO classification (Federation International de Gynécologie et d'Obstétrique). Complex examination included pelvic examination, colposcopy, cytological and histological tests. The cervical canal and the exterior part of cervix uteri epithelium scraping samples served as study materials.

Detection and genotyping of HPV DNA was carried out via the real-time PCR method using a RotorGene 6000 device (Corbett Research, Australia) and Amplisens® reagent sets (Amplisens® HPV HCR-screen-titre-FL, Cat.# R-V31-T-4x (RG,iQ,Mx); Amplisens® HPV HCR-genotype-FL, Cat.# R-V25(RG,iQ,Mx) (Moscow, Russia). The presence of the following HPV genotypes was determined: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59. The viral load value was calculated in the genomic equivalent of HPV DNA/105 cells, the viral load threshold was set at 3 lg of HPV DNA/105 cells in a sample.

The Fisher's ratio test was applied to assess statistical relevance of differences in the qualitative attributes occurrence distribution between the groups. Survival rates were evaluated according to the Kaplan-Meier method.

RESULTS AND DISCUSSION

The presence of HPV+ cervical cancer associated with one or several types of HPV was verified for 84 patients (72.4%) whilst 32 patients (27.6%) were not diagnosed with HPV. HPV- patients underwent second material withdrawal, DNA purification, detection and genotyping of HPV DNA in examined samples. Absence of the viruses was verified as a result.

The patients were divided into 2 groups depending on the HPV contamination:

- group 1 – HPV+ patients (n=84), average age – 42.1±1.7 year old;
- group 2 – HPV- patients (n=32), average age – 45.5±1.6 year old.

The groups did not differ in terms of general clinical and pathologic findings: tumor size, lymphatic cancer spread and histotype (data not exposed).

Genotyping of HPV+ samples showed that HPV genotype 16 is present in 67.8% of cases. This complies with the literature data and results obtained earlier [9, 13]. HPV of types 33 and 31 was ranked the 2nd and 3d, respectively (22.6% and 20.2%) whilst according to the literature data HPV of type 18 as the 2nd is most spread in many areas of the world [9]. When determining the viral load (virus DNA concentration) in the examined samples, we noted the number of patients with low viral load (< 3 lg HPV DNA/105 cells) who were considered to have low risk of cervical cancer development [10], comprising 22.6% of the examined patient group. 77.4% of patients had high viral load (>3 lg HPV DNA/105 cells), which is the case for high risk of cervical cancer development. It is known that concentration or viral load of HVP DNA may reflect papilloma viral infection severity and treatment prognosis. If the valid and standardized sample withdrawal is the case, the viral load less than 105 GE of high-risk HPV in scraping or 103 GE/105 cells is considered to be low, because such viral load is almost never encountered in high-grade dysplasia and cervical cancer and is associated with the minimal risk of their development. On the other hand, the viral load of more than 105 GE/105 cells is described as high and is associated with a higher risk of high-grade dysplasia and is more often encountered in cervical cancer. Besides, monitoring of viral load may prove to be useful; a decreased number of HPV DNA by more than 1 lg can be a transitory infection marker. At the same time, the viral load growth in 3, 6 or 9 months after treatment may be a sign of relapse [11, 12].

Studying survival in the groups showed decrease of both overall and disease-free survival among HPV- patients diagnosed with cervical cancer. Fig. 1 and 2 demonstrate disease-free and overall survival of patients with cervical cancer: observation period of disease-free survival for HPV+ and HPV- patient groups amounted to 102 and 68 months; overall survival – 52 and 83 months respectively. 2-year disease-free survival in the groups was 92.0% and 73.0%, overall survival – 86.0% and 65.0%.

One may suggest that a more aggressive cervical cancer form prevalence among HPV- patients is no accident and a decrease in such patients' survival may be caused by different oncogenic mechanisms of cervical cancer, which may explain the differences in the disease outcome. Harima and co-authors state that HPV- cancer is a separate group and this particular subtype responds worst to radiotherapy [6]. The data on the matter dates back to 2006: HPV viral load in cervix uteri epithelium scraping of patients diagnosed with cervical cancer was examined before treatment. The results showed that the hierarchy of cervical cancer prognoses depending on its severity was

as follows: HPV+ tumors with high viral load, HPV+ tumors with low viral load and the worst prognoses occurred for HPV- tumors [4].

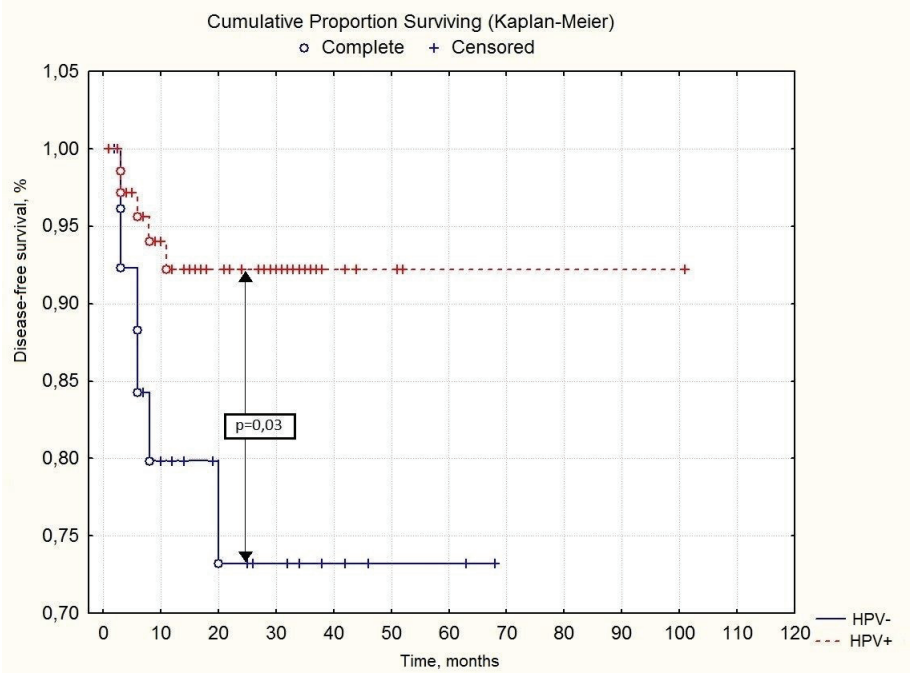

FIGURE 1. Relapse-free survival of patients diagnosed with cervical cancer

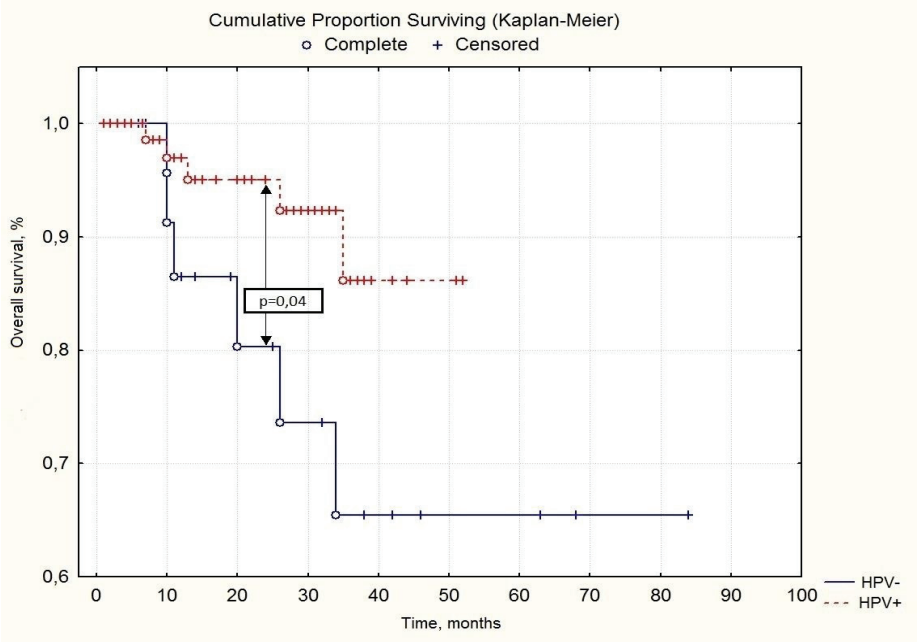

FIGURE 2. Overall survival of patients diagnosed with cervical cancer

CONCLUSIONS

Invasive cervical cancer is the second most common cancer among women worldwide and the most common female cancer in large areas of the developing world where an estimated 80% of new cases arise. Based on improvements in the HPV detection technology, it appears that an almost 100% HPV association is reached for cervical cancer. Studies in 22 countries coordinated by the International Agency for Research on Cancer (IARC) identified HPV DNA in almost all (99.7%) (of about 1000) cases of cervical cancer.

Factors which may explain rare cases in which no HPV DNA is detectable include improper sampling; disruption of HPV by integration events; the existence of still unidentified HPVs; sensitivity of the method; and the mechanism of transformation.

Finally, epidemiological studies identifying HPV independent risk factors are necessary to answer the question of whether HPV independent pathways exist for cervical carcinogenesis.

The current research has focused on the determinants of infection with oncogenic HPV types, the assessment of prophylactic and therapeutic vaccines, and the development of screening strategies incorporating HPV testing and other methods as adjunct to cytology. These are fundamental stepping stones for the implementation of effective public health programs aimed at the control of cervical cancer.

Nonetheless, HPV- cervical tumors occur 2.5 times less than HPV+ but they have significantly worse prognoses. The presence or absence of HPV DNA in a tumor may become a new independent prognostic factor for cervical cancer. HPV- cervical cancer pathogenesis is understudied and requires further and detailed research.

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