

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Prevalence of human papillomavirus in oropharyngeal squamous cell carcinoma in Serbia

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SUMMARY

Introduction/Objective Oropharyngeal carcinoma makes up to 3% of all newly diagnosed carcinomas in the world. In Serbia, oropharyngeal carcinoma constitutes 1.8% of all malignancies. Studies have shown a growing role of infections with human papilloma viruses (HPV) in oropharyngeal cancer etiology. HPV-positive patients have a more favorable prognosis and significantly higher rate of overall survival. The purpose of this paper was to establish how HPV status influenced Serbian patients' overall survival and the disease-free survival according to known risk factors (tobacco and alcohol consumption), clinical TNM stage of the disease, and modality of treatment.

Methods The study included 87 patients treated for oropharyngeal carcinoma in a one-year period with a five-year follow-up. Treatment modalities included surgery with or without postoperative radio- or chemoradiotherapy, only radiotherapy or chemoradiotherapy. Sex, common risk factors, TNM stage, and treatment method were considered, as well as the influence of HPV status on the overall survival and the disease-specific survival depending on the presence of risk factors.

Results HPV-positive patients with oropharyngeal carcinoma were more frequently men, smokers, and alcohol consumers. Considering clinical T, N, and M stage of the disease, the overall survival and the disease-specific survival rates were better in HPV-positive patients, who had better survival if they were treated with primary surgical therapy rather than primary radiotherapy.

Conclusion HPV status significantly influenced survival and locoregional control in Serbian patients with oropharyngeal carcinoma. This implies possible modifications of treatment strategies for these patients in order to further improve their prognosis and treatment outcomes.

Keywords: oropharyngeal carcinoma; human papillomavirus; overall survival; disease-specific survival

INTRODUCTION

Oropharyngeal squamous cell carcinoma (OPSCC) makes up to 3% of all newly diagnosed carcinomas in the world, with majority occurring in developing countries [1]. In Serbia, oropharyngeal carcinoma constitutes 1.8% of all malignancies. According to the latest available data from 2013, the ascertained incidence of diagnosed oropharyngeal squamous cell carcinoma in the general population of Serbia was 5.3/100,000 [2].

There have been changes in demographic characteristics, risk factors, and subsite of the OPSCC over the last few decades. Though they are still more frequent in men than in women, incidence was higher in younger white males, for human papilloma virus (HPV)-related cancers [3]. Subsites, like lingual and palatine tonsils, became more frequently involved, followed by the base of the tongue [4]. Studies in European countries and the United States have

shown a growing role of infections with HPV in increasing incidence of OPSCC [5]. In the United States, approximately 40–80% of oropharyngeal carcinomas are considered to be caused by HPV [6]. However, these patients have a more favorable prognosis and significantly higher rate of overall survival, with reported 50% improvement in the overall survival compared with HPV-negative patients [7, 8]. Studies that compare HPV status and outcomes of treatment in patients with OPSCC are trending in the literature, and this is the first study of that kind done on patients with oropharyngeal carcinoma in Serbia.

The purpose of this paper was to establish the demographic characteristics and risk factors in patients treated for OPSCC in Serbia, and to contemplate how HPV status influenced the patients' overall survival and disease-free survival taking into consideration clinical TNM stage of the disease and the modality of treatment.

Received • Примљено:
February 28, 2017

Revised • Ревизија:
October 23, 2017

Accepted • Прихваћено:
October 24, 2017

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METHODS

The study included 87 patients treated for OPSCC at the Clinic for Otorhinolaryngology and Maxillofacial Surgery of the Clinical Centre of Serbia in Belgrade in a one-year period (from January 2009 to January 2010). This study was approved by the Institutional Ethics Committee (440/IX-3/09), and all the patients signed the informed consent form prior to their inclusion in the study. The patients were divided into age groups according to the International Cancer Survival Standard using the Five Default Age Groups (15–44, 45–54, 55–64, 65–74, 75+) [9]. Risk factors such as continuous tobacco use and alcohol consumption during the follow-up period were also noted. The patients were treated after undergoing necessary diagnostic procedures (clinical examination, tumor biopsy, and histopathology verification, radiological diagnostics). Patients with previous treatment or relapse of the OPSCC were not included in the study. HPV positivity was estimated by positive p16 immunohistochemical staining of the tissue samples [10, 11]. The modality of treatment for every patient was decided on the Oncological Board (consisting of a radiotherapist, head and neck surgeons, an oncologist, and a histopathologist). The choice of primary and adjuvant treatment was decided based on the National Comprehensive Cancer Network and the American Society of Radiation Oncology guidelines, which are recommended and used at the Clinic for Otorhinolaryngology and Maxillofacial Surgery and the Institute for Oncology and Radiology of Serbia in Belgrade [12, 13]. Surgical therapy involved resection of the tumor with some form of neck dissection in case of cervical lymphadenopathy. Radiotherapy consisted of external radiotherapy with a total dose of 60–70 Gy in 30–35 fractions for six to seven weeks. The patients received chemotherapy concurrently with radiotherapy; three courses of cisplatin intravenously, on the first, fourth, and seventh week during radiotherapy. The follow-up period was five years. The patients were examined every month postoperatively during the first year, every three months during the second and third year, and every six months during the fourth and fifth year. Lethal outcome and relapse of the disease was noted in the follow-up period.

Overall survival and disease-free survival in HPV-positive and HPV-negative patients were analyzed depending on demographic data of the patients, such as age and sex, common risk factors, tobacco and alcohol use, T, N, M stage of the disease, and the modality of treatment. Overall survival and the disease-specific survival were assessed at one, three, and five years after the treatment.

IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA) was used for the data analysis. To determine demographic characteristics of the patients, descriptive statistics were used. The χ^2 test was used to compare monitored parameters between groups. Overall survival and the disease-specific survival were calculated according to the Kaplan–Meier method; the logrank test was used to compare survival parameters between patient groups. P-values lower than 0.05 were considered statistically significant.

RESULTS

The study comprised 69 (79.3%) males and 18 (20.7%) females of an average age of 59.64 years (SD \pm 8.46 years). HPV-positive patients were of an average age of 54.5, and HPV-negative of 64 years. The youngest patient was 35, and the oldest 82 years old. Continuous tobacco use during the follow-up period was noted in 53 (60.9%) of the patients, and 34 (39.1%) were non-smokers. Continuous consumption of alcohol during the follow-up period was noted in 47 (54%) of the patients, while 40 (46%) were non-drinkers. Forty-eight (55.2%) patients were HPV-positive. The patients were in different stages of the disease, without evident majority of the patients in a certain stage. Most of the patients were treated with surgery, followed by postoperative radiotherapy or chemoradiotherapy and concomitant chemoradiotherapy (Table 1).

Three-year and five-year overall survival was better for all age groups in HPV-positive patients, but the difference wasn't statistically significant. Overall survival was better for male patients who were HPV-positive after one-, three-, and five-year periods, and for women who were

Table 1. Characteristics of the patients included in the study

Parameter	HPV-negative n (%)	HPV-positive n (%)	Total n (%)
Age (years)			
45	2 (2.3)	3 (3.4)	5 (5.8)
45–54	3 (3.4)	15 (17.2)	18 (20.7)
55–64	23 (26.4)	17 (19.6)	40 (46)
65–74	16 (18.4)	5 (5.8)	21 (24.1)
\geq 75	3 (3.4)	0 (0)	3 (3.4)
Sex			
male	34 (39.1)	35 (40.2)	69 (79.3)
female	13 (14.9)	5 (5.8)	18 (20.7)
Smoking			
Smokers	27 (31)	26 (29.9)	53 (60.9)
Non-smokers	20 (23)	14 (16.1)	34 (39.1)
Alcohol			
Consumers	23 (26.4)	24 (27.6)	47 (54)
Non-consumers	24 (27.6)	16 (18.4)	40 (46)
T stage			
T1	8 (9.2)	6 (6.9)	14 (16.1)
T2	9 (10.3)	13 (14.9)	22 (25.2)
T3	12 (13.8)	15 (17.2)	27 (31)
T4	17 (19.6)	7 (8)	24 (27.6)
N stage			
N0	19 (21.9)	11 (12.6)	30 (34.5)
N1–3	28 (32.2)	29 (33.3)	57 (29.9)
M stage			
M0	44 (50.7)	37 (42.5)	81 (93.2)
M1	3 (3.4)	3 (3.4)	6 (6.8)
Treatment			
OP	7 (8)	2 (2.3)	9 (10.3)
RT	5 (5.8)	3 (3.4)	8 (9.2)
OP + RT or OP + RT/CH	24 (27.6)	19 (21.9)	43 (49.5)
RT/CH	12 (13.8)	15 (17.2)	27 (31)

RT – radiotherapy; RT/CH – chemoradiotherapy; OP – surgery

Table 2. Overall survival for HPV-negative and HPV-positive patients depending on their age, sex, tobacco use, alcohol consumption, TNM stage, and treatment modality

Parameter	1-year overall survival (%)		3-year overall survival		5-year overall survival		p
	HPV-negative	HPV-positive	HPV-negative	HPV-positive	HPV-negative	HPV-positive	
Age (years)							
45	50	100	50	50	50	50	0.038
45–54	66.7	92.3	66.7	46.2	33.3	38.5	
55–64	73.9	100	56.5	76.9	56.5	76.9	
65–74	75	100	62.5	80	56.3	60	
≥ 75	100	/	66.7	/	66.7	/	
Sex							
Male	62.9	96.8	45.7	64.2	45.7	56.7	0.042
Female	83.3	100	83.3	80	83.3	60	
Smoking							
Smokers	55.6	100	40.7	59.4	40.7	37.8	0.001*
Non-smokers	90	92.9	75	85.1	75	85.1	
Alcohol							
Consumers	76.2	95.7	61.9	66.2	61.9	56	0.558
Non-consumers	65.4	100	50	66.7	50	58.3	
T stage							
T1	100	100	100	83.3	85.7	66.7	0.002*
T2	92.3	100	84.6	87.5	84.6	62.5	
T3	69.2	92.3	46.2	67.1	46.2	67.1	
T4	35.7	100	21.4	57.1	21.4	28.6	
N stage							
N negative	78.9	100	68.4	100	68.4	85.7	0.018*
N positive	64.3	96.2	46.4	52.2	46.4	48.2	
M stage							
M0	68.9	96.9	55.6	65.4	55.6	54.5	0.531
M1	100	100	50	75	50	75	
Treatment							
OP	100	100	60	100	60	100	0.006*
RT	100	100	60	100	20	100	
OP+RT or OP+RT/HT	82.6	100	73.9	64.4	73.9	58	
RT+HT	33.3	90	13.3	64.3	13.3	64.3	

OP – surgery; RT – radiotherapy; RT/CH – chemoradiotherapy;

*p < 0.05

HPV-positive after a one-year period. However, this difference was not statistically significant (logrank test, $p = 0.042$) (Table 2). In addition, overall survival was better for HPV-positive non-smokers one, three, and five years after the treatment (logrank test, $p = 0.001$). Alcohol consumers and non-consumers who were HPV-positive had better overall survival rates after periods of one year and three years, but it was not statistically significant (logrank test, $p = 0.558$) (Figure 1).

Overall survival for patients who were HPV-positive was better compared to those who were HPV-negative for T1, T3, and T4 stage after one-, three-, and five-year periods (logrank test, $p = 0.002$) (Table 2). Overall survival was better in both groups of patients for those who had metastatic lymph nodes (96.2 vs. 64.3 for the period of one year, 52.2 vs. 46.4 for three years, and 48.2 vs. 46.4 for the period of five years), and in those without metastatic lymph nodes who were HPV-positive (100 vs. 78.9 for for the period of one year; 100 vs. 68.4 for three years, and 85.7 vs. 68.4 for the five-year period), compared to HPV-negative patients (logrank test, $p = 0.018$) (Figure 2). Significantly better

overall survival was detected in HPV-positive patients treated with radiotherapy (logrank test, $p = 0.006$). HPV-positive patients had better overall survival one, three, and five years after the treatment if the primary treatment was surgery and chemoradiotherapy (Figure 2).

Disease-free survival was better for almost all age groups in HPV-positive patients, except in patients younger than 45 years, but the difference between the HPV-positive and HPV-negative groups was not statistically significant. Disease-free survival in HPV-positive male patients was better, compared to HPV-negative patients (96.8 vs. 80.3 for the period of one year, 76.7 vs. 58.4 for three years, and 72.2 vs. 58.4 for the five-year period, $p = 0.153$). Considering continuous smoking during the follow-up, HPV-positive patients had significantly better disease-free survival rates compared to HPV-negative ones (logrank test, $p = 0.04$). Alcohol consumption did not significantly influence the overall survival in our patients, although survival was higher in HPV-positive patients one year (95.7 vs. 88.9) and three years after the treatment (78.3 vs. 72.2) (Figure 3).

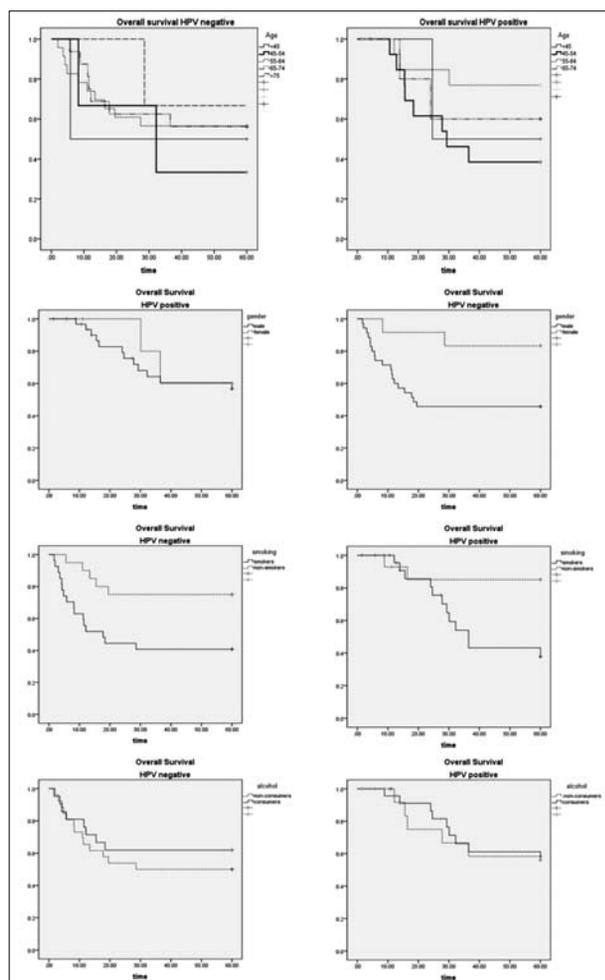


Figure 1. Kaplan–Meier curves for overall survival for HPV-negative and HPV-positive patients depending on age, sex, tobacco use, and alcohol consumption

Disease-free survival for patients who were HPV-positive was better than in those who were HPV-negative for T1, T2, and T4 stage after one-, three-, and five-year periods (Table 3). Disease-free survival was better for HPV-positive patients with metastatic lymph nodes (96.2 vs. 64.3 for the one-year period, 52.2 vs. 46.4 for the three-year period, and 48.2 vs. 46.4 for the five-year period), compared to HPV-negative patients. Disease-free survival was worse in HPV-positive patients without metastatic lymph nodes than in those who were HPV-negative five years after the treatment (logrank test, $p = 0.002$). Regarding the M stage, better disease-free survival was again detected in the HPV-positive group of patients (Figure 4). Significantly better disease-free survival was detected in HPV-positive patients treated with radiotherapy after three- and five-year periods, compared to HPV-negative patients (100 vs. 60 for the three-year period and 100 vs. 20 for the five-year period (log rank test, $p = 0.006$). HPV-positive patients had better overall survival one year, three years, and five years after treatment if the primary treatment was surgery and chemoradiotherapy (Figure 4).

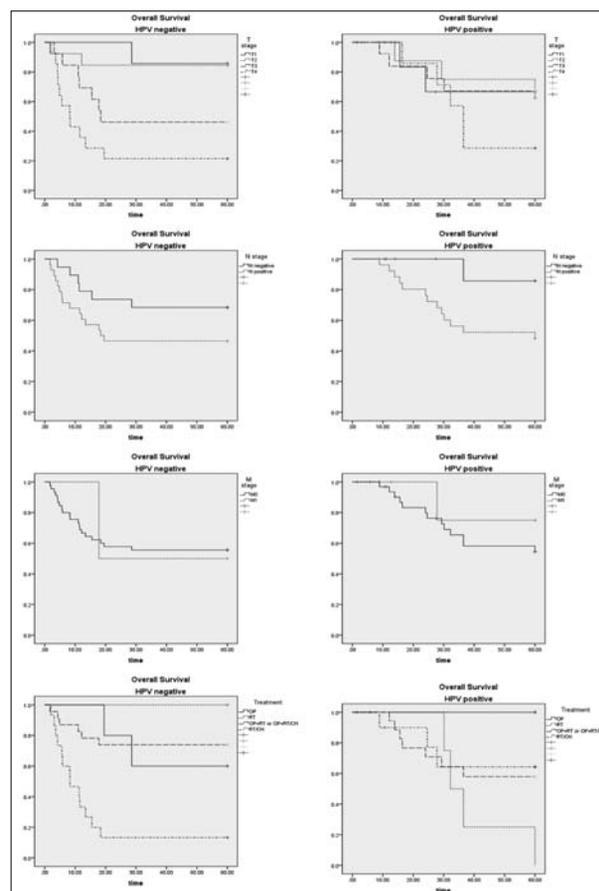


Figure 2. Kaplan–Meier curves for overall survival for HPV-negative and HPV-positive patients depending on the TNM stage and treatment modality

DISCUSSION

The correlation between outcomes and survival in patients with OPSCC with HPV positivity has been demonstrated in many studies [14, 15, 16]. No research was done in Serbia concerning this matter until the present study.

There were no significant differences between demographic characteristics in our study, comparing HPV-positive and HPV-negative patients. HPV-positive patients treated for OPSCC were more likely to be men (40.2%), smokers (26.4), and alcohol consumers (27.6%). In the HPV-positive group, women were less frequent (5.8% vs. 14.9%). Others studies documented the same findings, though it is noticed in the literature that the incidence of women diagnosed with OPSCC is rising [16, 17]. This trend is expected to demonstrate itself in the Serbian population as well.

Earlier research showed overall worse prognosis for active smokers with head and neck carcinoma, regardless of their HPV status [18, 19]. In our study, overall survival and the disease-free survival were better in HPV-positive patients who were not smokers. On the other hand, after a five-year follow-up period, HPV-negative smokers had better disease-free survival than non-smokers did, but no sig-

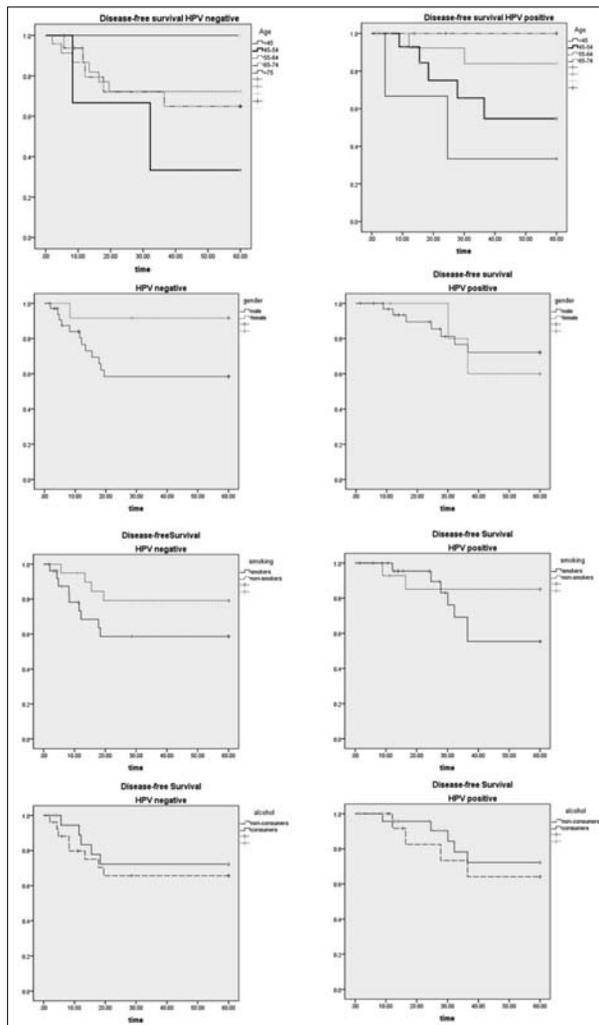


Figure 3. Kaplan–Meier curves for disease-free survival for HPV-negative and HPV-positive patients depending on age, sex, tobacco use, and alcohol consumption

nificant effect of smoking on the disease-free survival was detected. Similar results were published by Liskamp et al. [20]. Poorer results in smokers were attributed to hypoxia, microvascular damage, the immune suppressive effect of tobacco, and smoking-induced genetic alteration. Benson et al. [21] accounted age and tobacco for only 9% variation in overall survival by HPV status. The degree of cellular deregulations and response to therapy were proven to have bigger influence on improved prognosis in HPV-positive compared to HPV-negative patients. Alcohol consumption was not proven significant in overall and disease-free survival in our study, although some researches indicate that HPV positivity in non-drinking patients is a negative predicting factor [22].

Considering clinical T, N, and M stage of the disease, many studies to date have stressed better overall, disease-specific, and progression-free survival rates in HPV-positive OPSCC patients than in HPV-negative patients [14, 16, 23, 24]. This was observed in our study as well, except for some discrepancies in the three-year disease-free survival for T3 stage and in the five-year overall survival in T1 and T2 stages. These finding in our patients could be explained by lethal outcome caused by diseases other than cancer. Some publications identified advanced T stage (3 or 4) as a significant risk factor for overall survival, especially in HPV-negative patients [5, 14, 23]. On the other hand, N stage did not prove to be a statistically significant risk factor for overall survival, but rather extranodal spreading of the disease [14, 23]. In this study, disease-free survival was significantly longer in HPV-positive patients in advanced stages of the disease with positive nodal disease, compared to HPV-negative patients.

In our study, HPV-positive patients treated primarily with radiotherapy had better overall and disease-free survival compared to HPV-negative patients. A systematic

Table 3. Disease-free survival for HPV-negative and HPV-positive patients depending on their age, sex, tobacco use, alcohol consumption, TNM stage and treatment modality

Parameter	1-year disease-free survival (%)		3-year disease-free survival		5-year disease-free survival		p
	HPV-negative	HPV-positive	HPV-negative	HPV-positive	HPV-negative	HPV-positive	
Age (years)							
45	100	66.7	33.3	33.3	33.3	33.3	0.074
45–54	66.7	92.9	33.3	65.7	33.3	54.7	
55–64	86.7	100	72.3	83.9	72.3	83.9	
65–74	86.5	100	72.1	100	64.9	100	
≥ 75	100	/	100	/	100	/	
Sex							
Male	80.3	96.8	58.4	76.7	58.4	72.2	0.153
Female	91.7	100	91.7	80	91.7	60	
Smoking							
Smokers	73.3	100	58.7	69.2	58.7	55.4	0.040*
Non-smokers	90.7	94.1	81.1	74.8	81.1	74.8	
Alcohol							
Consumers	88.9	95.7	72.2	78.3	72.2	72.3	0.442
Non-consumers	95	92.9	79.2	85.1	79.2	85.1	

T stage							
T1	100	100	100	100	100	100	0.000*
T2	100	100	91.7	100	91.7	100	
T3	100	92.3	88.9	67.1	66.7	67.1	
T4	42.2	100	25.3	57.1	25.3	28.6	
N stage							
N0	94.1	100	94.1	100	94.1	88.9	0.002*
N1–N3	76.5	95.8	51	65.7	51	60.2	
M stage							
M0	82.7	96.9	69.4	77.3	69.4	68.7	0.976
M1	100	100	50	75	50	75	
Treatment							
OP	100	100	80	100	80	100	0.006*
RT	100	100	60	100	20	100	
OP + RT or OP + RT/HT	90.9	100	81.3	87.7	81.3	78.9	
RT + HT	55	90	22	64.3	22	64.3	

OP – surgery; RT – radiotherapy; RT/CH – chemoradiotherapy;

*p < 0.05;

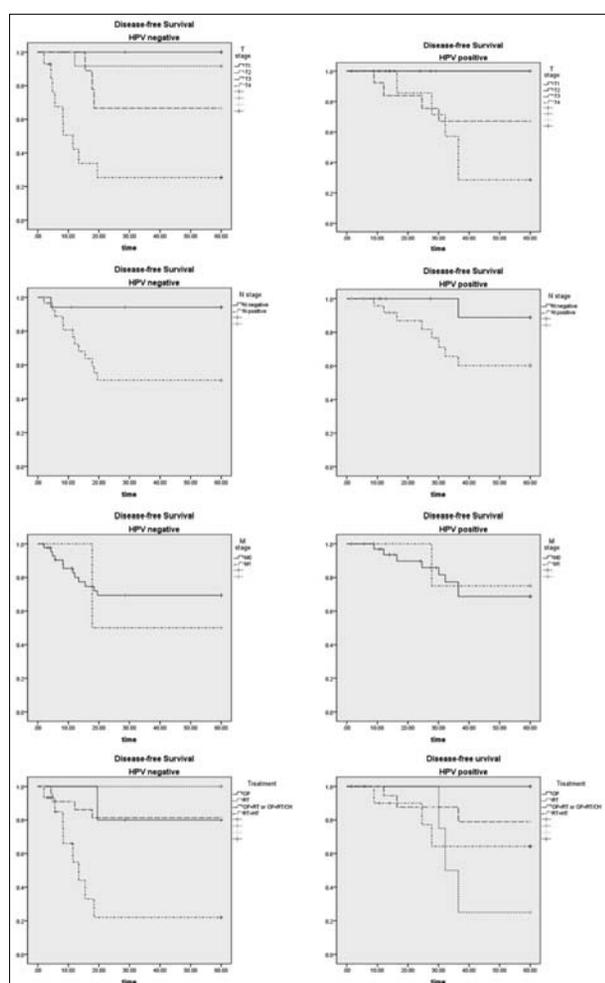


Figure 4. Kaplan–Meier curves for disease-free survival for HPV-negative and HPV-positive patients depending on the TNM stage and treatment modality

review, done in 2015, claimed better response rates to radiotherapy in HPV-positive patients, even in T3–4 tumors [25]. Also, for HPV-positive OPSCC patients, overall and disease-free survival was better if their primary treatment

was surgical therapy rather than radiotherapy, which was confirmed by results. It was suggested that HPV-negative patients have poorer response to multimodality treatment than HPV-positive patients [26]. In addition, some studies indicated that HPV-positive patients after being treated with chemoradiotherapy had significantly longer time to distant metastatic failure compared to HPV-negative patients [27]. Considering patients treated with surgery and adjuvant radiotherapy or surgery with adjuvant chemoradiotherapy in our study, no significant differences were noted between the HPV-positive and HPV-negative groups. The management of locoregionally advanced oropharyngeal cancer still focuses on definitive chemoradiotherapy. In addition to organ preservation, concomitant chemoradiotherapy can offer significant improvement in the five-year overall survival in poor-prognosis tumors and survival could be prolonged up to 16% [28].

Given all the advances in understanding the role of HPV infection in OPSCC pathogenesis, treatment, and outcomes, new strategies are needed to achieve better results. Some recent studies suggested deintensification of therapy for low-risk patients (HPV-positive patients who smoke less than 10 pack years, and have low volume tumors). Proposed methods of deintensification include decreasing doses of radiation (de-escalation) or replacing cisplatin radio-sensitization to targeted therapy with cetuximab [29]. Minimally invasive surgical techniques are extensively used for the management of early-stage tumors, and they involve transoral robotic surgery and transoral laser microsurgery. Tumors previously resected through external and extensive surgical approaches are now being treated by the transoral approach with less morbidity and complications, achieving satisfactory locoregional control [30].

CONCLUSION

In our study, no significant differences between demographic characteristics were found in comparing HPV-positive and HPV-negative patients' overall survival and

disease-free survival. HPV-positive non-smokers had better overall survival and the disease-free survival. They also had better overall survival and disease-free survival depending on the clinical TNM stage of the disease. Due to significant influence of HPV positivity on survival and locoregional control of the disease, introduction of better

diagnostic and therapeutic strategies in Serbia is needed. Routine detection of HPV should be done in all patients diagnosed with OPSCC before undergoing a specific oncology treatment. In addition to satisfactory oncological results, this would result in less morbidity, improved quality of life, and benefits to the patient.

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Учесталост хуманог папилома вируса у орофарингеалном планоцелуларном карциному у Србији

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САЖЕТАК

Увод/Циљ Орофарингеални карцином чини око 3% ново-дијагностикованих карцинома на свету. У Србији 1,8% болесника са малигнитетом болује од орофарингеалног карцинома. Студије указују на све већу улогу инфекције хуманим папилома вирусом (ХПВ). У литератури је показано да болесници који су позитивни на инфекцију ХПВ-ом имају бољу прогнозу и значајно веће укупно преживљавање.

Циљ овог рада је био да установи како ХПВ статус утиче на укупно преживљавање и преживљавање без знакова болести болесника са орофарингеалним карциномом у Србији, у зависности од познатих фактора ризика (конзумирање алкохола и цигарета), клиничког ТНМ стадијума и начина лечења.

Методe У студију је укључено 87 болесника којима је дијагностикован орофарингеални карцином током периода од једне године, са петогодишњим периодом праћења. Терапија је укључила хируршко лечење са постоперативном радиотерапијом или хемиорадиотерапијом, само радиотерапију или само хемиорадиотерапију. Испитивани су пол,

фактори ризика, клиничка ТНМ класификација, као и утицај ХПВ статуса на укупно преживљавање и преживљавање без знакова болести у зависности од присуства фактора ризика.

Резултати Болесници са орофарингеалним карциномом позитивни на ХПВ најчешће су били мушког пола, пушачи и конзументи алкохола. Што се тиче клиничког ТНМ стадијума, преживљавање је било боље код ХПВ позитивних болесника. Боље преживљавање су имали ХПВ позитивни болесници лечени примарно хируршки у односу на оне примарно лечене радиотерапијом.

Закључак ХПВ статус значајно утиче на преживљавање и локорегионалну контролу код болесника са орофарингеалним карциномом у Србији. Ова чињеница указује на потребу модификовања терапијских стратегија за ове болеснике, у циљу даљег побољшавања прогнозе њихове болести и исхода терапије.

Кључне речи: орофарингеални карцином; хумани папилома вирус; укупно преживљавање; преживљавање без знакова болести