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Analysis of results of radiotherapy for oropharyngeal cancer

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ABSTRACT

Introduction: Smoking and alcohol consumption remain the two most important risk factors for the development of oropharyngeal tumours, but there is an increasing number of younger patients (age <50 years) with human papillomavirus (HPV) association origin, also known as positivity. The role of radiotherapy (RT) in the treatment of this disease is paramount. *Aim:* To describe the radiotherapy results for oropharyngeal tumours and to search for prognostic parameters that influence the response of these malignant lesions to radio-chemotherapy. *Methods:* 95 patients underwent definitive radio- or radio-chemotherapy (RCT) for histologically squamous cell, oropharyngeal carcinoma at our Institute between 1 January 2019 and 31 December 2020, of which 51 (54%) received the latter. The mean age was 61.9 years (37–82 years) and the male-female ratio was 69:26. The average total dose was 69 Gy (range: 54–70 Gy). *Results:* The 5-year local control (LC), cancer-specific survival (CCS), and overall survival (OS) calculated by the Kaplan-Meier method were 71, 69, and 58%, respectively. Forty-four cases (46%) were confirmed to have HPV involvement. HPV positive (+) tumours showed significantly better behaviour compared to HPV negative (−) cases in LC, CCS and OS. Smoking had a significant negative effect on cure rates: LC, CCS and OS were better in non-smokers. A significant negative effect of smoking on survival was also observed in HPV-associated cases. For HPV- lesions, RCT had a stronger effect on LC than RT alone (64 vs 43%, $P = 0.03$). *Conclusions:* HPV-associated malignancies show better survival outcomes to radio ± chemotherapy than their HPV- counterparts. In all cases, smoking worsens the response to treatment. For HPV- tumours, chemotherapy with radiation, compared to irradiation alone, has a more significant effect on survival outcomes, whereas for HPV+ tumours this effect is less pronounced.

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KEYWORDS

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INTRODUCTION

Malignancies in the head and neck region were the sixth most common type of tumours worldwide in 2020 [1]. It can be said that while the incidence of oral cavity tumours (lip, gingiva, etc.) in the region has decreased recently, the incidence of oropharyngeal tumours is one of the most intensively increasing tumour type in developed countries, mainly due to the spread of human papillomavirus (HPV) [1, 2]. Interestingly, 71% of carcinomas in this area in the United States of America are HPV-associated [2].

Concerning the etiology of oropharyngeal cancers, two important triggers should be mentioned: Firstly, smoking and alcohol consumption, as in other squamous cell carcinomas of the head and neck region, and secondly, HPV virus infection [2, 3]. HPV-associated neoplasms have a more favourable prognosis and are more sensitive to radiotherapy (RT) due to their lower differentiation, reduced repair mechanisms and faster redistribution [4]. The improved prognosis has also led the American Joint Committee on Cancer to define a separate staging system for the two types of tumours [5].

Patients with oropharyngeal cancer usually present to their doctor with complaints of swallowing, prolonged throat pain, neck swelling, and spitting up blood, and may be diagnosed by physical examination, sampling, and imaging [5]. Therapy may include surgery, RT, and drugs. With the development of surgical techniques, transoral laser microsurgery (TLMS) and transoral robotic surgery (TORS) have come to the fore, after which, depending on the histology, the majority of patients also receive radio(chemo)therapy to target lower locoregional tumour recurrence [5]. However, to preserve swallowing and speech functions, organ-preserving definitive radio(chemo)therapy remains the most widely chosen therapeutic modality to date [6].

In the following retrospective study, we analysed the outcome of oropharyngeal tumours with definitive radio(chemo)therapy and investigated several prognostic factors affecting survival, with a particular focus on the role of HPV virus.

MATERIALS AND METHODS

Between January 1, 2019 and December 31, 2020, the data of 95 patients with histological squamous cell carcinoma of oropharyngeal origin – who received definitive RT or radio-chemotherapy (RCT) – were available in the medical system at the National Institute of Oncology. RCT was performed in 51 (54%) patients. The average age of the patients was 61.9 years (range: 37–82 years) and the male-female ratio was 69:26. The average total dose of RT was 69 Gy (range: 54–70 Gy). During the treatment and this retrospective analysis all procedures were carried out in compliance with the Declaration of Helsinki and conformed to the ethical standards of human experimentation in Hungary.

According to the institute's protocol, patients were scheduled for a clinical examination every 3 months for the first 2 years, and every 6 months thereafter, and for a routine imaging

examination (computed tomography/CT/ or magnetic resonance imaging /MRI/) every 6 months. The response to irradiation was assessed by CT or MRI 2–3 months after the end of radiotherapy. Any residual local or regional disease (including any patient with a response less than the overall response) was considered a failure. Survival time was calculated from the time of initial treatment.

STATISTICAL ANALYSIS

Treatment success was described by the parameters of local control (LC), locoregional control (LRC), overall survival (OS), and cancer-specific survival (CCS). For statistical calculations, we analysed the survival probabilities of patients using the Kaplan-Meier method [7]. The starting point was the end of the treatment from which we represented the different survival lines. Differences in survival were compared using a log-rank test. Cox regression models were used to examine the potential risk factors for LC, LRC, OS, and CCS [8]. A significance level of $P \leq 0.05$ was specified.

RESULTS AND DISCUSSION

The median follow-up time for surviving patients was 45.1 months (range 31–56), and we were able to follow all patients. Histology confirmed HPV involvement in 46% ($n = 44$) of the cases. The median age of patients was 61 years for patients with HPV+ tumours and 62.6 years for HPV-negative patients. HPV association was confirmed in 90.1% of patients under 50 years of age. Tumours were detected at Stage I in 23.2%, Stage II in 24.2%, Stage III in 21% and Stage IV in 31.6%. In advanced Stage (III–IV) HPV+ cases, 90% received RT with concurrent chemotherapy, compared with 66.7% of HPV- patients ($n = 28$). This difference may be due to the better health conditions of HPV+ cancer patients, which allowed them to receive chemotherapy. The proportion of smokers in the overall population was 71%, compared to 45% for HPV+ cancer patients and 92% for HPV- cases. 60% of HPV- cancer cases also regularly consumed alcohol in addition to smoking. The clinicopathological characteristics of the patients are shown in Table 1.

The 5-year probabilities of LC, LRC, OS, CCS were 71%, 67%, 69% and 58%, respectively. HPV-associated tumours showed significantly better clinical behaviour compared to HPV- cases: LC 88% vs 55% ($P = 0.005$), LRC 86% vs 49% ($P = 0.0016$), CCS 83% vs 54% ($P = 0.008$), OS 79% vs 40% ($P = 0.0004$) (Fig. 1). This correlation was also found to be true for locally more advanced tumours (T3-4): LC with 48% ($P = 0.02$), LRC with 51% ($P = 0.015$), CCS with 38% ($P = 0.06$), OS with 56% ($P = 0.005$) were better for HPV+ tumours.

The two groups of tumours were treated generally with the same dose of radiation (mean dose was 69 Gy, range: 54–70 Gy), therefore the two populations were very similar in terms of side effects: at least Grade III dysphagia and mucositis, as acute side effects, were observed in 34% and 26% of patients with HPV+ and HPV- tumours, respectively ($P = 0.43$), while late side effects (beyond 3 months after treatment) were found in 50% and 41% of patients, respectively (at least Grade 2 xerostomia and dysphagia) ($P = 0.48$).

Smoking had a significant, but negative effect on cure rates: LC was better in non-smokers by 36% ($P = 0.0004$) and OS by 50% ($P = 0.0001$). 45% of patients with HPV-associated tumours

Table 1. Clinicopathological parameters of 95 patients with oropharyngeal tumours treated with (C)RT

Parameters	Number of cases (%)
Histology (squamous cell carcinoma)	95 (100)
HPV status	
HPV+	44 (46)
HPV-	51 (54)
Grading	
Grade I	10 (11)
Grade II	55 (58)
Grade III	30 (31)
Sex	
Female	26 (27)
Male	69 (73)
Extent of tumour	
T1	14 (15)
T2	40 (42)
T3	28 (29)
T4	13 (14)
Spread to lymph nodes	
N0	30 (32)
N1	22 (23)
N2	37 (39)
N3	6 (6)
Stage	
Stage I	22 (23)
Stage II	23 (24)
Stage III	20 (21)
Stage IV	30 (32)

($n = 20$) were smokers and their chances of cure were also significantly impaired by their harmful addiction: LC was 96% vs 79% ($P = 0.1$), LRC 96% vs 73% ($P = 0.004$), CCS 96% vs 66% ($P = 0.02$), and OS 92% vs 61% ($P = 0.03$). Regular alcohol consumption further worsened the chances of cure in HPV- tumour patients, LC was better in the non-alcohol-consuming population by 24% ($P = 0.23$), LRC by 36% ($P = 0.09$), CCS by 27% ($P = 0.15$), and OS by 25% ($P = 0.2$).

RCT produced better results compared to RT alone, but there was no significant difference for either parameter: LC was 77% vs 65% ($P = 0.11$), LRC 71% vs 62% ($P = 0.15$), CCS 63% vs 53% ($P = 0.23$), and OS 75% vs 62% ($P = 0.14$). However, when looking at stage III–IV tumours, we found a more significant difference in the success rates of the two therapeutic modalities (LC: 69% vs. 44%/$P = 0.04$/, LRC: 60% vs. 44%, /$P = 0.08$/, OS: 50% vs. 37% /$P = 0.2$/, CCS: 66% vs. 37% /$P = 0.02$/). The two therapeutic modalities were similarly successful in HPV+ tumours for LC and LRC: 94% vs. 87% ($P = 0.47$) and 87% vs. 87% ($P = 0.9$), respectively, whereas HPV- tumours responded better to RCT than to RT: LC 64% vs. 43% ($P = 0.03$), LRC 53% vs. 43% ($P = 0.1$). OS was found to be superior to RCT regardless of HPV association.

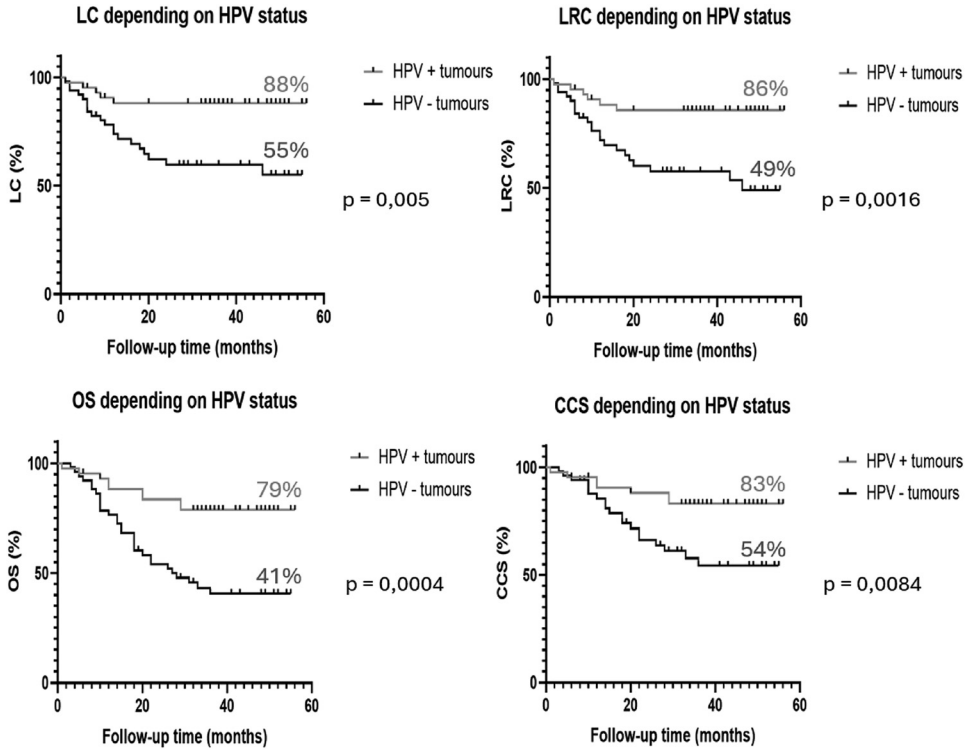

Fig. 1. The 5-year local control (LC), locoregional control (LRC), overall survival (OS) and cancer-specific survival (CCS) depending of human papillomavirus (HPV) status

There was no significant effect of age (±50 years), sex, "grading" on survival parameters.

Our research confirms that the prognosis of squamous cell carcinomas of the oropharynx is influenced by the HPV status of the tumour, the patient's harmful habits (smoking, alcohol consumption) and the therapeutic modality used (RT or RCT). In our study, HPV association was confirmed in 91% of tumours in patients younger than 50 years of age, which is in line with the worldwide trend that HPV is responsible for many oral carcinomas in young people [9].

In order to compare our results with other studies, we analysed the literature of HPV-associated oropharyngeal cancers from the last 20 years. The improved prognosis of oral carcinomas with HPV association has been demonstrated in recent years by several clinical studies. Ang KK et al. [10] identified HPV status, smoking, lymph node status (for HPV+ tumours) and primary tumour extension (for HPV- cases) as the most important factors determining patient survival. In their study, they performed a follow-up of 323 patients with HPV status and found significantly better behaviour of HPV-associated tumours concerning 3-year outcomes (OS: 82% vs. 57%, LRC: 86% vs. 65%, progression-free survival: 74% vs. 43%) ($P < 0.001$) [10]. In addition, they observed that each pack/year of smoking increased the chance of tumour recurrence by 1%, regardless of HPV status [10].

Posner MR. et al. [11] described that HPV+ tumours showed significantly less locoregional recurrence than their HPV- counterparts (16% vs. 49%, $P = 0.0002$), and thus justified that these tumours also had significantly better OS outcomes (82% vs. 35%, $P < 0.0001$). In a 2014 clinical trial, it was also shown that even at 8-year follow-up, better behaviour was found in p16-positive (usually associated with HPV positivity) neoplasms (OS: 71% vs 30%, LRC: 79% vs 48%, $P \leq 0.0006$), and although the primary tumour led to death at similar rates in the two groups of patients, secondary malignancy was more often the cause of death in patients with p16-negative tumours [12].

Liskamp CP et al. [13] used the results of their study to call attention to the need to include smoking cessation in the treatment of patients with HPV+ tumours, as they found significantly worse 3-year outcomes among active smokers (LRK: 86% vs. 67%, $P = 0.02$). This finding is supported by the 5-year results obtained in our study (LRK: 96% vs. 73%, $P = 0.04$).

The recognition that HPV-associated tumours have a more favourable prognosis has led in recent years to the need to reduce the doses of RT and chemotherapy treatments in the hope of reducing toxicity [14]. This is particularly important because the percentage of these tumours among oropharyngeal tumours has increased from 41% before 2000 to 72% in 2009 and is still increasing, therefore many patients could benefit from the new protocol [15]. Several clinical trials are currently underway in this regard [16, 17].

Chen AM. et al. [18] treated 44 advanced (stage III-IV) HPV+ patients with reduced doses of radiation (54 Gy or 60 Gy instead of the usual 70 Gy) after 2 cycles of induction chemotherapy, and their 2-year results were very promising (LRC: 95%, progression-free survival: 92%). Grade 3 or more severe mucositis was observed in only 15% of patients [18].

Eisbruch A. et al. [19] observed that every 10 Gy of radiation above 55 Gy delivered to the upper and middle musculus constrictor pharyngis significantly increases the chance of developing dysphagia. In their 2021 clinical trial, Yom SS et al. [20] used reduced doses of radiation in a preselected group of patients (HPV+ oropharyngeal tumour, <10 pack/year smoking and good health condition). Both treatment protocols they studied achieved a pre-specified progression-free survival of at least 85% for two-year outcomes (IMRT /60Gy/ + cisplatin: 91%, IMRT /60Gy/: 88%), and patients' 1-year swallowing function also met the MD Anderson Dysphagia Intervention (MDADI) scale score of at least 60 [20].

Although the possibility of replacing cisplatin given simultaneously with radiotherapy with cetuximab in the hope of milder side effects seemed promising, the drawbacks of this approach have been demonstrated in several studies [21–23]. One is the study by Rischin D. et al. [21], in which 189 randomised patients were assigned to two groups in order to show that the two therapeutic approaches are associated with similar severity of side effects, but the oncological outcomes are worse with cetuximab (3-year relapse-free survival: 80% vs 93%, $P = 0.015$) [21]. The DE-ESCALate HPV trial [22] also demonstrated that the introduction of cetuximab instead of cisplatin did not reduce the incidence of either severe or all-grade toxicity at two-year follow-up, and that CRT produced significantly better overall survival outcomes (97.5% vs. 89.4%, $P = 0.001$) compared with adding biologic therapy to radiotherapy. Furthermore, the RTOG 1016 study [23] also showed that locoregional recurrence was more frequent in the group of patients receiving cetuximab therapy (17.3% vs. 9.9%, $P = 0.0005$) and 5-year progression-free survival was significantly worse in this population compared to those receiving CRT (67.3% vs. 78.4%, $P = 0.0002$).

With the evolution of surgical techniques, TORS and TLM treatment (usually complemented by adjuvant therapy) has emerged as a real competitor to definitive radio(chemo)therapy for

oropharyngeal tumours [24]. Zorzi SF. et al. [25] found the two therapeutic modalities to be similarly effective in advanced-stage (stage III-IV) HPV-associated cancers (TORS +- adjuvant therapy: OS: 97%, definitive radio(chemo)therapy: OS: 98%) and described it promising that in one-third of the patients from group „A" no adjuvant therapy was required after TORS, thus reducing side effects.

For advanced (stage III-IV) oropharyngeal tumours, concomitantly administered RCT is the preferred treatment modality over RT alone [26]. Recognising the increased radiosensitivity of HPV+ lesions in recent years, Chen AM. et al. have shown good results in treating HPV-associated head and neck tumours with irradiation alone (3-year LRC: 90%, OS: 83%), which are consistent with the results expected from RCT [27, 28]. When further stratifying patients by stage, these values were 88% and 81% for stages III and IV, respectively [26]. Yamamoto Y. et al. [29], looking at locally advanced oropharyngeal tumours, also described that RT alone can be as successful as the RCT approach in HPV+ cases.

Our results are similar to those reported in other publications on this topic. Our study confirms a better prognosis for HPV-associated tumours, with 5-year results showing 88% LC, 86% LRC, 79% OS and 83% CCS. This association was also found to be true for locally advanced (T3-4) oropharyngeal tumours (LRK: 80%, OS: 70%). Regardless of HPV status, the effect of smoking on patients' chances of recovery was found to be significantly negative. Our study confirms the principle that RCT is the preferred treatment modality over RT alone for advanced stage tumours, but HPV+ tumours also showed an excellent response to RT alone, in synchrony with the results of many other studies [28, 29]. Overall, similar to other publications, we advocate the continuation of deintensification studies in HPV-associated oropharyngeal tumours, specifically in low-risk, non-smoking patients.

Conflicts of interest: None.

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