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# Trends in the treatment of human papillomavirus-associated oropharyngeal carcinoma in Slovakia

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The optimal treatment of oropharyngeal cancer (OPC) associated with human papillomavirus (HPV) is currently a subject of clinical research. This questionnaire study investigated current trends in the treatment of HPV-associated (HPV+) OPC in Slovakia with the incorporation of deintensification of oncological treatment into routine clinical practice outside of clinical trials. The Slovak Cooperative Head and Neck Cancer Group (SCHNCG) developed a questionnaire aimed at identifying trends in the oncological treatment of HPV+ OPC intended for all radiation oncology (RO) facilities in Slovakia. Specialists in the field of RO responded to general questions about the character of their individual institutions as well as to 4 theoretical clinical scenarios (case reports) regarding the treatment of HPV+ OPC, focusing primarily on the applied dose of radiotherapy (RT), the extent of target volumes, and the type of concurrent chemotherapy (CHT). The questionnaire study involved 35 RO specialists from 14 institutions in Slovakia. Regarding primary chemoradiotherapy (CRT) in T1N1M0 HPV+ OPC, 16 respondents (45.7%) would consider de-escalation of the RT dose to <70 Gy. In the case of postoperative RT in pT1pN1M0 HPV+ OPC with negative resection margins (R0) and absent extracapsular extension (ECE), 4 physicians (11.4%) would consider de-escalation of the RT dose to <60 Gy in the tumor bed area, while the majority of the treating specialists (n=19, 54.3%) would omit concurrent CHT. In the case of primary RT in elderly patient with T2N1M0 HPV+ OPC, the same number of physicians (n=16, 45.7%) would consider de-escalation of the RT dose to <70 Gy, and 14 respondents (40.0%) would completely omit CHT. In a high-risk patient with T2N3M0 HPV+ OPC with a complete response after 3 cycles of induction chemotherapy (iCHT), none of the respondents would indicate a reduction in the RT dose to the area of the original tumor and lymphadenopathy to <60 Gy. The doses and extent of irradiated volumes in the treatment of HPV+ OPC in Slovakia vary among different institutions. The tendency to de-escalate RT doses and reduce doses of concurrent systemic therapy in Slovakia is high and there was also an observed trend to reduce the extent of radiation treatment fields.

*Key words: oropharyngeal cancer, human papillomavirus, radiotherapy, treatment deintensification, de-escalation of chemoradiotherapy*

Head and neck cancers (HNC) represent the sixth most common malignancy worldwide and are typically associated with the consumption of tobacco and alcohol products [1]. Oropharyngeal cancer (OPC) associated with the carcinogenic human papillomavirus (HPV) infection represents a specific biological entity with a distinct etiology, biological behavior, and prognosis [2]. The incidence of HPV–associated (HPV+) OPC is rapidly increasing, especially in developed countries, and its distribution within individual states has a typical pandemic–like character, with the maximum of patients concentrated in urban areas [3]. It is the most common HPV–associated malignancy, surpassing even cervical cancer in its incidence [4]. Considering the anatomical arrangement of the oropharynx, this type of carcinoma most commonly arises from the area of palatine tonsils and the base of the tongue [4]. Oral HPV infection is transmissible via kissing, oral sex, or contact of the mouth with the anorectal region, making HPV+ OPC the fastest-spreading sexually transmitted disease in the world [5]. The most significant high-risk HPV strains causing HPV+ OPC are HPV 16, 18, 31, 33; however, the most common causative agent of HPV+ OPC is the HPV 16 subtype [6]. The standard markers of HPV infection include immunohistochemical staining for the presence of the p16 protein

or direct detection of the HPV deoxyribonucleic acid (DNA) using in situ hybridization or polymerase chain reaction (PCR) [7]. Considering the significantly better overall survival (OS) outcomes in the patients with HPV+ OPC compared to patients with HPV-negative (HPV–) OPC, a unique staging system for HPV+ OPC was established in the 8th edition of the TNM classification of malignant tumors in 2017, reflecting the excellent prognosis and distinct biological behavior of this tumor entity [8]. A majority of cases are diagnosed in stage I or II, where long-term OS is observed globally [9]. The improvement of OS is achieved due to a better local control (LC), determined also by a higher radiosensitivity of HPV+ OPC [10].

Current curative treatment options in HPV+ OPC include minimally invasive surgery or RT, which may be combined with chemotherapy (CHT) in selected clinical situations. Deintensification of primary treatment methods with the aim of long-term post-treatment toxicity reduction and quality of life (QoL) improvement in the survivors have become the key points of many clinical studies; however, current recommendations for the treatment of HPV+ OPC worldwide do not differ from the treatment strategies in HPV– OPC [11]. The aim of this questionnaire study is to identify national trends in Slovakia in the willingness to de-escalate the dose and reduce the extent of primary or postoperative RT and concurrently administered CHT and the dose and extent of RT after induction CHT (iCHT) in selected clinical situations in case of a patient with excellent performance status and in elderly comorbid patient.

## Materials and patients

To determine the current treatment trends in the management of HPV+ OPC in Slovakia, an anonymous questionnaire of the Slovak Cooperative Head and Neck Cancer Group (SCHNCG) was designed for board-certified specialists in the field of radiation oncology (RO). The questionnaire was sent by mail in March 2023 to all RO facilities in Slovakia, with the number of copies sent corresponding to the number of RO specialists at each facility. The individual responses (data) were collected in March–April 2023. The SCHNCG questionnaire included four clinical scenarios in the treatment of HPV+ OPC, focusing primarily on the doses and extent of irradiated volumes prescribed and planned by individual specialists, as well as the dose and type of concurrent CHT. The major task of the questionnaire survey was to assess the individual preference of RO specialists, not a specific preferred practice in the individual RO institutions.

**Case report 1:** primary chemoradiotherapy (CRT) in a 40-year-old non-smoker with Karnofsky Performance Status (KPS) 100 and normal renal functions, with HPV+ OPC of the right tonsil T1N1M0 measuring 17×15×19 mm (Figure 1A). The tumor was located >1.5 cm from the midline, and there were 2 affected cervical lymph nodes (LN) in levels II and III on the right side of the neck.

**Case report 2**: postoperative CRT in a 42-year-old light smoker (<10 pack-years) with KPS 100 and normal renal functions, with HPV+ OPC of the left base of the tongue base following transoral tumor resection with negative resection margins (R0) and modified radical neck dissection (ND) on the left and elective ND on the right (levels II–IV), pT1pN1 M0 (Figure 1B). There were 2 affected LNs in level II on the left measuring 18×19 mm and 21×25 mm without signs of extracapsular extension (ECE). Thirteen LNs were examined on the left, and 8 LNs were examined on the right, with clinically and pathologically negative findings on the right side of the neck.

**Case report 3:** primary CRT in a 75-year-old polymorbid non-smoker with KPS 70 and HPV+ OPC of the left tonsil measuring 34×44×45 mm with a bulky lymphadenopathy (LAP) in levels II–III on the left side of the neck measuring 48×58×56 mm, T2N1M0 (Figure 1C). The patient had a long-term treatment for arterial hypertension and chronic ischemic heart disease.

**Case report 4:** RT following iCHT in a 56-year-old non-smoker with KPS 90 with normal renal functions and HPV+ OPC of the right tonsil measuring 25×30×40 mm with a bulky LAP in levels II–IV on the right side of the neck measuring 58×60×75 mm, T2N3M0 (Figure 1D). The patient achieved a CR after 3 cycles of iCHT based on docetaxel, cisplatin, and fluorouracil (TPF) which was verified using a positron emission tomography/computed tomography (PET/CT) scan (Figure 1E).

For each respondent, the tendency towards treatment deintensification was assessed; specifically, the de-escalation of the dose of primary or postoperative RT or reduction of the extent of irradiated fields, and the willingness to reduce the dose of concurrently administered CHT in each institution. The R statistical software version 4.3.1 was used for standard summary statistics as median and range for continuous variables and numbers and percentages for categorical variables. This study was a non-interventional questionnaire study and was approved by the ethical committee of the primary investigator (ID LEC-RS050324).

## Results

**Surveyed population.** Altogether, 35 RO specialists out of 14 institutions in Slovakia participated in this questionnaire study. The response rate (RR) was 31.3% (35/112) of the total number of radiation oncologists working in the field and 93.3% (14/15) of the total number of institutions that provide curative RT in Slovakia. A detailed analysis of the surveyed population is included in Table 1.

### Primary RT in HPV+ OPC T1N1M0 (case report 1)

The extent of radiation treatment fields in case report 1 according to the responses from the RO specialists is shown in Figure 2A.

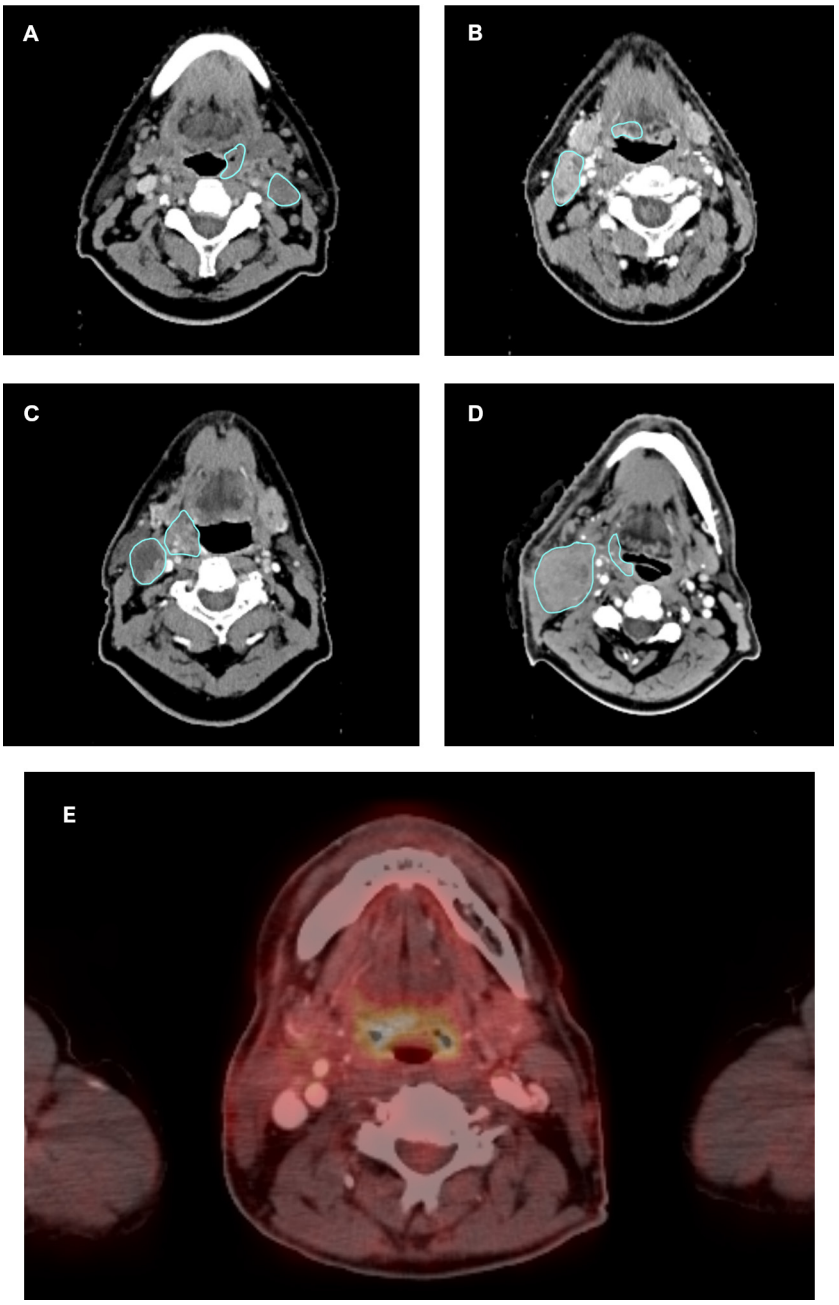



**Figure 1. Imaging studies of (A) the T1N1M0 of the right tonsil case report, (B) the pT1N1 M0 left base of the tongue case report, (C) the T2N1M0 of the left tonsil case report, (D) initial T2N3M0 right tonsil case report and (E) radiologic response after induction chemotherapy. The light blue line represents gross tumor volume delineation.**

All respondents would include the area of the involved right tonsil (tumor gross tumor volume, GTVt) and the two involved ipsilateral LNs (nodal gross tumor volume, GTVn) into the high-risk planning target volume (HR PTV). A standard 70 Gray (Gy) dose would be applied by 19 respondents equally in GTVt and GTVn, 2 physicians would use the dose >70 Gy and >60 Gy in both GTVt and GTVn. Eleven respondents would de-escalate the dose to 60 Gy in both GTVt and GTVn. Three physicians would treat the regions of GTVt and GTVn using different doses with a tendency to de-escalate the dose in GTVt to 66 Gy and the dose in GTVn to 60 Gy (Figure 2B, 2C). The ipsilateral uninvolved LNs would be treated to a dose of >54 Gy and <60 Gy by 12 respondents, the dose of 60 Gy would be indicated by 11, the

dose of 54 Gy would be equally indicated by 11 physicians and the dose of <54 Gy and ≥45 Gy would be indicated by 1 specialist (Figure 2D). The contralateral uninvolved LNs would be included in the radiation field by 29 physicians out of which 12 would treat the area using 54 Gy, 15 specialists would treat the area using <54 Gy and >45 Gy, and 2 respondents would use 45 Gy. The contralateral uninvolved neck would not be treated by 6 RO specialists (Figure 2A, 2E). Concurrent systemic treatment would be indicated by 34 respondents exclusively with the use of a platinum-based cytotoxic agent. Fifteen respondents would opt for high-dose cisplatin 100 mg/m$^2$ administered every 3 weeks and 19 respondents would opt for weekly administered cisplatin. The dose of the cisplatin administered weekly would be 40 mg/m$^2$ in 9 respondents. Ten physicians would reduce the dose of weekly administered cisplatin to <40 mg/m$^2$ and 1 specialist would completely omit any systemic treatment in this clinical case (Figure 2F).

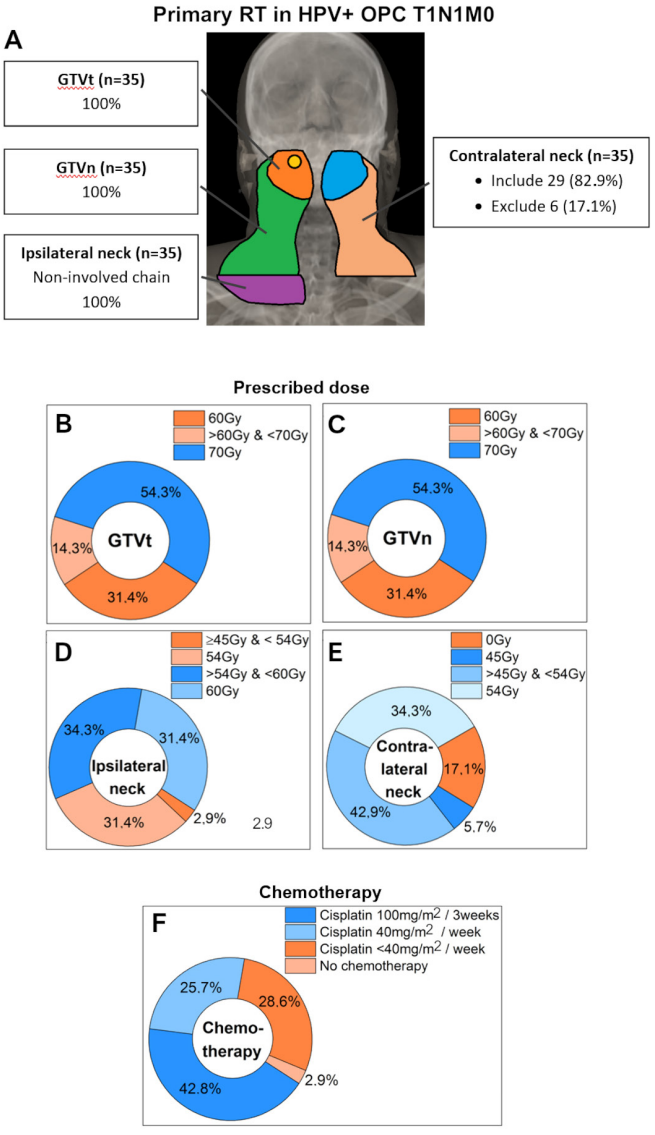
**Table 1. Characteristics of the respondents (n = 35)**

| Characteristic | Number (%) |
|---|---|
| Length of clinical practice (years) | |
| 5–10 | 4 (11.4) |
| 10–15 | 5 (14.3) |
| 15–20 | 5 (14.3) |
| >20 | 21 (60.0) |
| Patients treated annually with EBRT in the institution | |
| <500 | 9 (25.7) |
| 500–1000 | 17 (48.6) |
| >1000 | 9 (25.7) |
| Patients treated annually with EBRT for HPV+ OPC | |
| <5 | 3 (8.6) |
| 5–10 | 9 (25.7) |
| 11–20 | 11 (31.4) |
| >20 | 10 (28.6) |
| | 2 (5.7) responses N/A |
| Indication of the treatment in patients with HPV+ OPC* | |
| multidisciplinary team | 15 (42.9) |
| interdepartmental referral | 17 (48.6) |
| individual RO specialist | 3 (8.6) |
| ENT surgeon | 6 (17.1) |
| RT technique in the treatment of HPV+ OPC* | |
| 3-D CRT | 1 (2.9) |
| IMRT | 4 (11.4) |
| VMAT | 34 (97.1) |
| combination of various techniques | 1 (2.9) |
| | 1 (2.9) response N/A |
| Availability of surgical treatment of HPV+ OPC within the hospital/institution | |
| yes | 19 (54.3) |
| no | 16 (45.7) |
| Availability of TORS within the hospital/institution | |
| yes, and TORS is used in the treatment of HPV+ OPC | 4 (11.4) |
| yes, but TORS is not used in the treatment of HPV+ OPC | 0 (0) |
| no | 31 (88.6) |
| Availability of TOLS within the hospital/institution | |
| yes, and TOLS is used in the treatment of HPV+ OPC | 5 (14.3) |
| yes, but TOLS is not used in the treatment of HPV+ OPC | 5 (14.3) |
| no | 24 (68.6) |
| | 1 (2.9) response N/A |
| Surgical treatment of the primary tumor* | |
| transoral non-robotic (TOS) | 17 (48.6) |
| transoral robotic (TORS) | 3 (8.6) |
| transoral laser (TOLS) | 4 (11.4) |
| external approach; transcervical - lateral, medial, lateromedial pharyngotomy | 7 (20.0) |
| external approach; transmandibular | 5 (14.3) |
| combination of approaches | 8 (22.9) |
| | 12 (34.3) responses N/A |
| Expansion of the concentric CTV to PTV margin (mm)* | |
| 3 mm | 9 (25.7) |
| 4 mm | 3 (8.6) |
| 5 mm | 24 (68.6) |
| 6 mm | 0 (0) |
| 7 mm | 0 (0) |

**Table 1.** ***Continues ...***

| Characteristic | Number (%) |
|---|---|
| Adaptive replanning at weight loss and change of the volume of the neck during RT | |
| yes | 29 (82.9) |
| no | 6 (17.1) |
| Protocol of IGRT* | |
| planar MV imaging | 3 (8.6) |
| planar kV imaging | 24 (68.6) |
| CBCT | 20 (57.1) |
| | 1 (2.9) response N/A |
| Enteral feeding during RT* | |
| prophylactic PEG before initiation of RT | 22 (62.9) |
| reactive PEG in severe dysphagia | 18 (51.4) |
| reactive NGT in severe dysphagia | 5 (14.3) |

*more than 1 answer available; Abbreviations: RT – radiotherapy, HPV – human papillomavirus, OPC – oropharyngeal cancer, RO – radiation oncologist, ENT – ear, nose, throat, 3-D CRT – 3-dimensional conformal radiotherapy, IMRT – intensity-modulated radiotherapy, VMAT – volumetric-modulated arc therapy, TORS – transoral robotic surgery, TOLS – transoral laser surgery, CTV – clinical target volume, PTV – planning target volume, IGRT – image-guided radiotherapy, MV – megavolt, kV – kilovolt, CBCT – cone-beam computed tomography, PEG – percutaneous endoscopic gastrostomy, NGT – nasogastric tube, N/A – not available.




## Postoperative RT in HPV+ OPC pT1N1 M0 (case report 2)

The extent of radiation treatment fields in case report 2 according to the responses from the RO specialists is shown in Figure 3A.

In this clinical case, all respondents would irradiate the tumor bed area. A majority of the respondents (n=21) would irradiate the tumor bed using a standard dose of 60 Gy; 10 physicians would escalate the dose in the tumor bed area despite R0 resection to >60 Gy. Four respondents would de-escalate the radiation treatment dose in the tumor bed area; 3 specialists would treat the tumor bed using a dose of <60 Gy and >54 Gy, and 1 respondent would treat this area using 54 Gy (Figure 3B). A majority of the respondents (n=25) would include upper jugular LNs (level II) into the intermediate-risk clinical target volume (IR CTV) on the left side of the neck; middle jugular LNs (level III) would be included in this volume by 22 physicians and lower jugular LNs (level IV) would be included by 16 physicians. Lateral retropharyngeal (lateral RP) LNs would be included into IR CTV by 11 specialists, submandibular LNs (level IB) would be included by 9 physicians and deep cervical LNs (level V) would be included by 1 physician. The most commonly indicated dose in the IR PTV on the left would be <60 Gy and >54 Gy (n=13), the standard 60 Gy dose would be indicated by 10 physicians. De-escalation of RT dose in the IR-PTV on the left would be indicated by 12 specialists altogether, out of which 7 would use the dose of 54 Gy and 5 would apply the

**Figure 2. Distribution of RT field (A) and prescribed doses in doughnut plots according to the irradiated subsites in GTVt (B), GTVn (C), ipsilateral neck (D), and contralateral neck (E) and distribution of the dose and type of CHT (F) for definitive CRT in T1N1M0 disease. Orange-colored values represent doses lower than conventional. RT, radiotherapy, CRT, chemoradiotherapy, CHT, chemotherapy, GTVt, gross tumor volume – tumor, GTVn, gross tumor volume – nodal.**

dose of <54 Gy and ≥45 Gy. None of the specialists would indicate the dose of <45 Gy in the IR PTV on the left side of the neck (Figure 3C). A high proportion of the RO specialists (n=26) would include level IV LNs into the low-risk clinical target volume (LR CTV) on the left side of the neck, level III LNs would be included by 17, level IB LNs by 13, lat. RP LNs would be included by 11, and level II LNs by 9 specialists. One respondent would omit RT in the LR PTV on the left side of the neck. The most commonly indicated dose in the LR PTV on the left side of the neck would be the dose of <54 Gy and >45 Gy (n=19), 11 physicians would treat this volume using 54 Gy, and 4 physicians would indicate the dose of 45 Gy into this area (Figure 3D). A majority of the treating physicians (n=26) would include level IV LNs into the LR CTV on the right side of the neck, level III and II LNs would be equally included by 22 physicians. Four respondents would equally include level IB and lateral RP LNs and 3 respondents would include level V LNs into the LR CTV on the right. Seven specialists would completely omit RT on the right side of the neck. The most commonly indicated dose in the LR PTV on the right side of the neck would be the dose of <54 Gy and >45 Gy (n=14) 7 physicians would indicate the dose of 54 Gy, 45 Gy would be indicated by 6 physicians, and <45 Gy would be indicated by 2 treating specialists (Figure 3E).

Sixteen treating specialists would indicate concurrent systemic treatment, and all of these specialists would apply a platinum-based agent; high-dose cisplatin 100mg/m$^2$ administered every 3 weeks would be indicated by 12, weekly cisplatin 40 mg/m$^2$ would be indicated by 2, and weekly cisplatin <40 mg/m$^2$ would be equally indicated by 2 specialists. A majority of the respondents (n=19) would completely omit concurrent systemic treatment in this clinical case (Figure 3F).

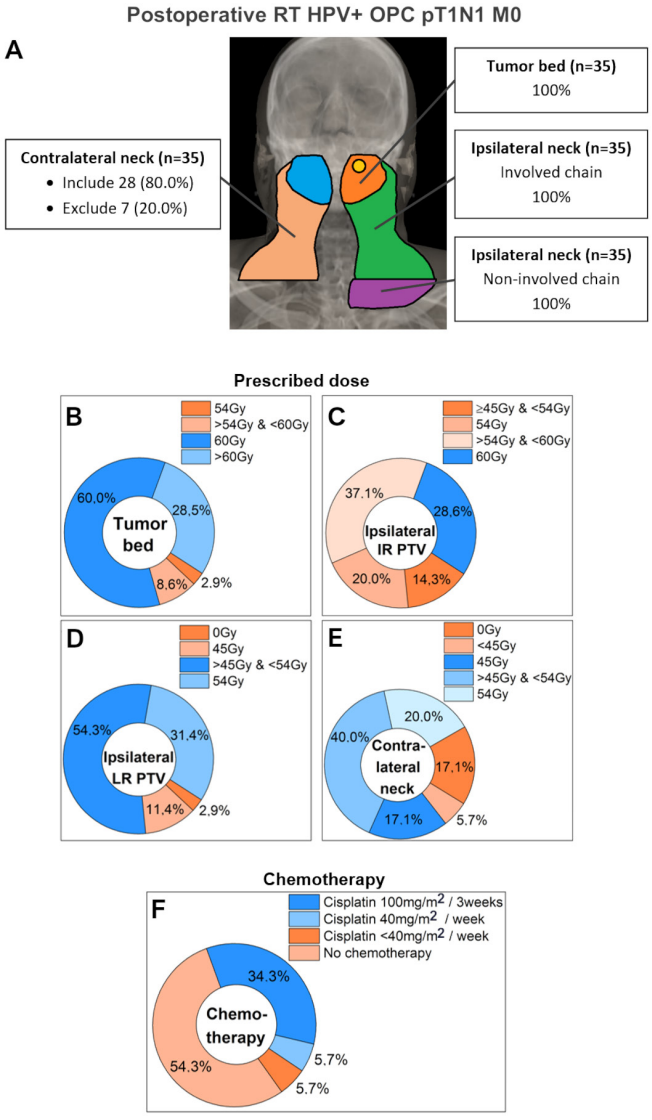



**Figure 3. Distribution of RT field (A) and prescribed doses in doughnut plots according to the irradiated subsites in the tumor bed (B), ipsilateral IR PTV (3C), ipsilateral LR PTV (D) and contralateral neck (E), and distribution of the dose and type of CHT (F) for postoperative CRT in T1N1M0 disease. Orange-colored values represent doses lower than conventional. RT, radiotherapy, CRT, chemoradiotherapy, CHT, chemotherapy, IR PTV, intermediate-risk planning target volume, LR PTV, low-risk planning target volume.**

## Primary RT in HPV+ OPC T2N1M0 in an elderly patient (case report 3)

In case report 3, a majority of the treating physicians (n=19) would indicate a standard 70 Gy dose equally in the GTVt and GTVn (HR PTV) areas. In the HR PTV, a de-escalated RT dose would be considered by 16 physicians; the dose of <70 Gy and >60 Gy would be indicated by 9, the dose of 60 Gy would be indicated by 6, and the dose of <60 Gy and >54 Gy would be indicated by 1 treating specialist (Figure 4A). Concurrent systemic treatment would be indicated by a majority of the treating physicians (n=21). Nine specialists would indicate weekly administered cisplatin 40 mg/m$^2$ and equally 9 physicians would indicate weekly administered cisplatin <40 mg/m$^2$. Two respondents would either use weekly administered cisplatin <40 mg/m$^2$ or weekly administered paclitaxel 30–40 mg/m$^2$ combined with carboplatin (area under the curve, AUC 2). One physician would indicate daily cisplatin 10 mg in total daily dose during the first 10 consecutive days of RT and 1 physician would indicate concurrent cetuximab. Fourteen specialists would completely omit concurrent systemic treatment in this clinical case (Figure 4B).

## Radiotherapy of HPV+ OPC T2N3M0 following iCHT (case report 4)

In case report 4, a majority of the respondents (n=34) would indicate RT of the pre-treatment extent of the tumor and regional LAP (HR CTV), 1 respondent would completely omit RT in this patient. Thirteen specialists would irradiate

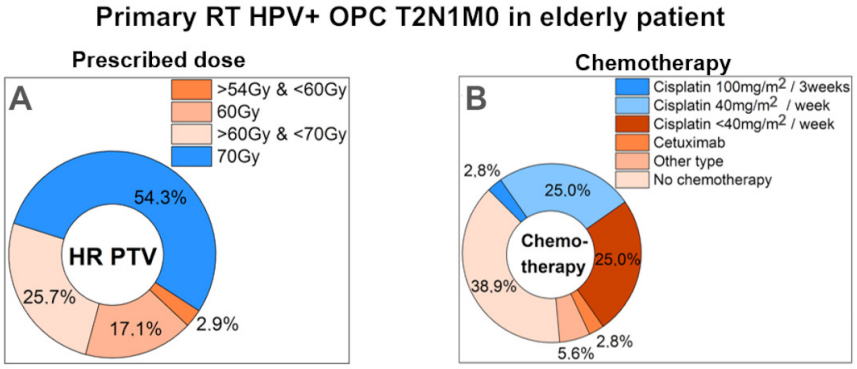



**Figure 4. Distribution of prescribed doses in doughnut plots according to the irradiated subsites in the HR PTV (A) and distribution of the dose and type of CHT (B) for definitive CRT in T2N1M0 disease in elderly patient. Orange-colored values represent doses lower than conventional. CRT, chemo-radiotherapy, CHT, chemotherapy, HR PTV, high-risk planning target volume.**

the HR PTV using the dose of 70 Gy, 11 respondents would use the dose of <70 Gy and ≥66 Gy, 4 respondents would use the dose of <66 Gy and >60 Gy, equally 4 respondents would use the dose of 60 Gy in the HR PTV. Two specialists would indicate different doses in the pre-treatment extent of the tumor (66 Gy) and in the pre-treatment regional LAP (59.4 Gy) (Figure 5).

A majority of the respondents (n=29) would include level IB LNs into the IR CTV on the ipsilateral side of the neck, level V and lateral RP LNs would be included equally by 27, retrostyloid (RS) LNs would be included by 23, and level II, III, and IV would be included equally by 16 treating physicians. The contralateral uninvolved side of the neck would be irradiated by a majority of the respondents (n=34). Thirty-two treating specialists would include level IV LNs into the contralateral LR CTV, 30 would equally include levels II and III, and 9 would include lat. RP LNs and 8 treating physicians would include level IB LNs into this area. One specialist would omit RT on the contralateral uninvolved side of the neck in case report 4.

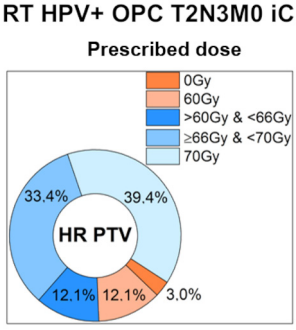



**Figure 5. Prescribed dose in doughnut plots according to the irradiated subsites in HR PTV for RT following iCHT with complete response in T2N3M0 disease. Orange-colored values represent doses lower than conventional. RT, radiotherapy, iCHT, induction chemotherapy, HR PTV, high-risk planning target volume.**

## Discussion

The incidence of HPV+ OPC has been increasing rapidly in the last years worldwide [1,3]. Many clinical studies brought evidence of a significantly better locoregional control (LRC) and OS in HPV+ OPC compared to HPV– OPC [12, 13]. These findings logically lead to a question of whether comparable treatment results could be reached via treatment deintensification that would offer a more favorable toxicity profile and could result in a significant improvement of the patients´ QoL during the treatment and after its completion.

Identification of the prognostic factors plays a pivotal role in the risk stratification of the patients and their safe accrual into the clinical trials. In a recursive partitioning analysis (RPA) of 721 patients with OPC, the association with HPV infection was the strongest independent factor of an improved OS [HPV+ vs. HPV–; hazard ratio (HR) 0.41, 95% confidence interval (CI) 0.29–0.57, p <0.001)]. A positive history of smoking and a higher pack-years count resulted in a significantly worse prognosis in HPV+ OPC similarly to a higher nodal stage of the disease (N-code). Other covariates with a negative impact on OS were higher age at the time of diagnosis (>50 years), non-white race, and a higher T-code of the disease. This RPA stratified patients into 3 subgroups where different yet homogenous OS values were observed; low-, intermediate-, and high-risk subgroups with a 3-year OS in 93.0%, 70.8%, and 46.2%, respectively [12]. Low-risk patients (non-smokers with an early-stage disease) are highly curable individuals and are ideal candidates for treatment deintensification clinical trials. High-risk patients (heavy smokers >10 pack-years with an advanced-stage disease) reach significantly worse OS results and should not be considered for clinical trials with treatment deintensification [12].

Regarding the excellent prognosis of HPV+ OPC, over the last decade, numerous strategies of treatment deintensification have been the key point of intensive scientific research

(minimally-invasive surgical techniques, de-escalation of the dose of primary or postoperative RT, reduction of the dose of concurrent CHT, substitution of cisplatin by another systemic agent with an expected more favorable toxicity profile, omission of concurrent CHT, administration of iCHT with a reduced dose of subsequent RT in responders) and numerous, mostly single-arm prospective studies with a low number of patients have been conducted; however, prospective randomized trials with a higher number of enrolled patients are still missing [9].

The actual data on the use of minimally invasive surgical methods in the treatment of HPV+ OPC come from a small number of retrospective single-arm studies. These studies confirmed excellent treatment results and safety of transoral robotic surgery (TORS) [14–18] and transoral laser microsurgery (TLM) with an elective ND in early stage T1–2 disease with a single involved LN <3 cm [19, 20]. A phase II prospective randomized study ORATOR that compared the treatment effect and toxicity profile in HPV+ OPC patients that had undergone primary TORS and elective ND vs. patients that had undergone primary intensity-modulated RT (IMRT) to a dose of 70 Gy, brought evidence on similar OS and progression-free survival (PFS) with excellent function preservation (mostly swallowing) in both groups [21]. However, up to 71% of the patients that had undergone primary TORS, were indicated to postoperative RT or CRT, and the unimodal character of the treatment, which could have played a pivotal role in the treatment deintensification, could not have been preserved. In Slovakia, the overall availability of TORS in HPV+ OPC is low (4 respondents from 1/15 of the tasked institutions in this study) (Table 1) and, in a majority of cases, other than robotic surgical techniques are used in the treatment of HPV+ OPC.

In an effort to optimize the treatment of HPV+ OPC, several studies have focused on the reduction of primary RT dose that could result in the reduction or elimination of postoperative complications and organ function preservation. A randomized phase II study ORATOR2 compared the efficacy of primary TORS plus elective ND followed by postoperative IMRT (in a reduced dose of 50 Gy/25 fractions or 60 Gy/30 fractions in case of positive resection margins or ECE) to the efficacy of primary de-escalated IMRT 60 Gy with a weekly administration of cisplatin 40 mg/m$^2$ [22]. Patients treated with primary de-escalated IMRT reached superior 2-year OS and PFS compared to the patients treated with primary TORS (100% vs. 89% and 100% vs. 84%). The patient accrual in ORATOR2 had been suspended due to unusual and rare complications resulting in 2 deaths in the patients that had undergone primary TORS that brought upon concerns about the quality of the surgical treatment and subsequent postoperative RT [23]. In a prospective non-randomized phase II study published by Chera *et al.* in 2018, patients with T0-3 N0-2c (American Joint Committee on Cancer – AJCC 7. edition) HPV+ OPC with minimal smoking history were treated with a primary de-escalated IMRT 60 Gy with a weekly administered cisplatin 30 mg/m$^2$. The results of 3-year LC, regional control (RC), cause-specific survival (CSS), and OS were 100%, 100%, 100%, and 95%. The reduction of RT dose and the dose of concurrent CHT in this study resulted in excellent treatment results with a high QoL preservation in the survivors [24]. In another randomized phase II study, NRG-HN002, 306 patients with T1-T2 N1-N2b and T3 N0-N2b (AJCC 7. edition) HPV+ OPC with ≤10 pack-years were treated with primary de-escalated IMRT 60 Gy (6 weeks) with concurrent weekly cisplatin 40 mg/m$^2$ (arm A) or with accelerated IMRT 60 Gy (5 weeks) without concurrent CHT (arm B). The results of 2-year PFS and OS were 90.5% and 96.7% vs. 87.6% and 97.3% in arms A and B, respectively. A higher rate of locoregional failure (LRF) had been reported in arm B compared to arm A (10% vs. 3%) [25]. The effort to reach maximum LRC is the reason why many clinical trials investigating the optimal treatment of HPV+ OPC use CRT rather than RT alone. In this questionnaire study, up to 45.7% of the respondents preferred de-escalated primary RT in a low-risk non-smoker with KPS 100, and the same result was observed in the case of a low-risk elderly patient.

A high rate of low-risk HPV+ OPC patients indicated to primary CRT may benefit from the reduction of the dose of concurrent cisplatin. In a non-randomized phase II study, 114 patients with T0-3 N0-N2c (AJCC 7th edition) HPV+ OPC with a limited history of smoking (<10 pack-years) were treated with primary de-escalated IMRT (60 Gy, 6 weeks) with or without concurrent reduced cisplatin 30 mg/m$^2$ (6 weekly doses). Patients with a low-risk disease received RT alone and patients with an intermediate- and high-risk disease were indicated to CRT with a reduced dose of CHT. The 2-year LRC, PFS, and OS altogether were 95%, 86%, and 95%, with no reported severe long-term toxicity [26]. These encouraging results confirmed a high efficacy of primary de-escalated RT or CRT with a reduced dose of concurrent CHT that can result in excellent treatment outcome with a substantial reduction of treatment-related side effects and this strategy proved itself worthy of further investigation. In this questionnaire study, the tendency to omit concurrent CHT was significantly higher in the case of the elderly patient (14 respondents) compared to the case of the younger patient with KPS 100 (1 respondent). In contrast, the tendency to administer high-dose cisplatin 100 mg/m$^2$ was much higher in the younger patient with KPS 100 (15 respondents) compared to the elderly comorbid patient (1 respondent). The tendency to reduce the dose of concurrent CHT <40 mg/m$^2$ was similar in the elderly patient (9 respondents) compared to the younger patient (10 respondents).

Epidermal growth factor receptor inhibitor, cetuximab, offers a potentially less toxic alternative to cisplatin. Two multicentric prospective randomized phase III trials evaluated its safety and efficacy in the primary oncological treatment of HPV+ OPC; the study De-ESCALATE included 334 eligible patients with low-risk HPV+ OPC with a zero

or limited history of smoking (<10 pack-years). The patients were randomly assigned to the arm with concurrent cisplatin 100 mg/m$^2$ day 1, 22, and 43 (166 patients) or concurrent cetuximab 400 mg/m$^2$ induction dose followed by weekly 250 mg/m$^2$, 7 applications (168 patients) combined with IMRT 70 Gy/35 fractions. The 2-year adverse toxicity (primary endpoint) in both subgroups was not significantly different; however, the 2-year OS was significantly worse in the cetuximab group as well as the 2-year recurrence rate [27]. Another study, RTOG 1016, included 849 patients with T1-T2 N2a-N3 M0 (AJCC 7. edition) HPV+ OPC. All patients underwent primary accelerated IMRT 70 Gy/35 fractions (5 weeks). Patients either received concurrent cetuximab (arm A) induction dose 400 mg/m$^2$ followed by weekly 250 mg/m$^2$, 7 applications (425 patients) or concurrent cisplatin (arm B) 100 mg/m$^2$ day 1 and 22 or RT (424 patients). The results of acute and long-term toxicity were similar in both arms; however, the results of 5-year OS were 77.9% vs. 84.6% and the results of 5-year PFS were 67.3% vs. 78.4% in the cetuximab vs. cisplatin group [28]. These important phase III studies confirmed the superiority of cisplatin in the primary CRT of HPV+ OPC and the treatment scheme of cisplatin 100 mg/m$^2$ administered every 3 weeks remains a standard of care [11]. In this questionnaire study, none of the respondents would indicate concurrent cetuximab in primary CRT in the younger low-risk patient with T1N1M0 HPV+ OPC with KPS 100 and only 1 respondent would consider its administration in the elderly low-risk patient with T2N1M0 HPV+ OPC with KPS 70.

Patients with HPV+ OPC who undergo primary surgical therapy and are found to have high-risk factors in the definitive histopathological findings (positive resection margins, ECE, multiple positive LNs) are indicated to a standard postoperative RT (54–66 Gy in the intermediate- to high-risk areas) [11]. Several clinical studies intended to clarify the exact role of reduced postoperative RT in the treatment of HPV+ OPC, but the significance of this treatment approach remains unclear [14, 29–34]. A randomized phase II study ECOG 3311 evaluated therapeutic outcomes in patients with HPV+ OPC that had undergone primary TORS and were subsequently stratified into 4 subgroups; low-risk patients were indicated to observation (arm A), intermediate-risk patients were either indicated to de-escalated postoperative RT 50 Gy (arm B), or standard-dose RT 60 Gy (arm C). High-risk patients (positive resection margins, ECE, ≥5 positive LNs, single positive node >6 cm) were indicated for postoperative CRT in a standard dose of 60–66 Gy with weekly cisplatin 40 mg/m$^2$ (arm D). This study confirmed the safety and efficacy of TORS in the unimodal treatment of low-risk HPV+ OPC and the safety of bimodal treatment (TORS followed by de-escalated postoperative RT) in the patients with intermediate-risk HPV+ OPC [14, 30]. As TORS is not routinely performed in Slovakia, adoption of the ECOG 3311 study results is minimal. De-escalated postoperative RT with omission of the tumor bed from the irradiated volume (AVOID study) in patients with negative resection margins in another option of safe treatment deintensification in HPV+ OPC [32], however, in this questionnaire study, none of the respondents would have indicated omission of the tumor bed from within the irradiated volume in a low-risk pT1pN1 M0 HPV+ OPC with R0 resection in a patient with a limited history of smoking. In a non-randomized phase II study MC1273, a substantial de-escalation of the postoperative RT in the tumor bed area was used (from the standard 60–66 Gy to experimental 30–36 Gy) in selected patients with R0 resection and ≤10 pack-years. The 2-year OS and PFS were 98.7% and 91.0% and the 1- and 2-year adverse toxicity rates were 0% and 0% [33]. In this questionnaire study, however, none of the respondents would have indicated postoperative RT <54 Gy in the tumor bed area. To define the exact role of de-escalation of postoperative RT in the treatment of HPV+ OPC, a longer follow-up of the patients is of critical importance as well as the establishment of more prospective multicentric randomized trials with higher numbers of involved patients.

Despite years of clinical research, the exact role of iCHT followed by RT in the treatment of HNC remains unclear, except for the concept of organ preservation in patients that would otherwise be indicated to total laryngectomy, and a decrease in the rate of distant metastasis has also been observed with this treatment approach [9]. Regarding the toxicity of iCHT, which is not negligible and may in fact be very significant, it is controversial to label this treatment strategy as a real deintensification in the clinical practice. Specifically, in the HPV+OPC, several single-arm phase II studies have been conducted that focused on the de-escalation of RT based on the response to iCHT. In the ECOG 1308 trial, patients with stage III–IVA (AJCC 7th edition) HPV+ OPC were indicated to 3 cycles of iCHT (cisplatin, paclitaxel, cetuximab). Patients with a CR received RT 54 Gy/27 fractions (arm A) and patients with a partial response proceeded to a standard-dose RT 69.3 Gy in the pre-treatment GTVt and GTVn areas (arm B). The 2-year PFS and OS were 80% vs. 96% and 94% vs. 96% in arms A vs. B. Reduction of the RT dose led to a significant improvement in swallowing and nutritional status [34]. In a single-arm phase II study OPTIMA, patients with stage III–IVA (AJCC 7. edition) HPV+ OPC were indicated to 3 cycles of CHT (carboplatin and nab-paclitaxel) and proceeded to RT according to the risk group; low-risk patients with ≥50% response received RT 50 Gy (arm A), low-risk patients with 30–50% response or high-risk patients with ≥50% response received 45 Gy CRT (arm B). Non-responders we indicated to 75 Gy CRT (arm C). In the OPTIMA study, the reduction of treatment fields was also included; RT had been restricted to the adjacent groups of LNs only. The 2-year PFS and OS were 95% and 100% in low-risk patients and 94% and 97% in high-risk patients [35]. In this questionnaire study, none of the respondents would have indicated the reduction of the RT dose <60 Gy in the pre-treatment GTVt or GTVn

areas and the treatment fields would not have been reduced either (no omission of level IB or lat. RP LNs). The exact role of iCHT in the treatment of HPV+ OPC will have to be re-evaluated by prospective randomized trials; however, the rate of clinical response to iCHT remains a valuable prognostic biomarker.

Routine use of de-escalated RT in the standard clinical practice out of clinical trials was evaluated by a retrospective study of 617 patients with HPV+ OPC treated in various institutions in the USA. A de-escalated dose of RT was applied in 16.9% of cases, mostly in elderly comorbid patients. In the cohort of patients treated with de-escalated RT, the results of 3- and 5-year OS were 83% and 80%, and in the cohort of patients treated with a standard-dose RT, these values were 83% and 78% (p=0.83). The use of de-escalated RT in HPV+ OPC did not impact survival in the USA [36]. Another study that investigated trends in the treatment of HPV+ OPC in South Korea, was a questionnaire study conducted by the Korean Society for Head and Neck Cancer Treatment. In this study, 42 respondents from various Korean institutions took part out of which approximately 20% would de-escalate the dose of primary RT in T2N1M0 HPV+ OPC in the GTVt and GTVn areas, however, no tendency towards reduction of the treatment fields was observed. In the clinical case of a low-risk HPV+ OPC patient treated with primary surgery (pT2pN1 M0) with negative resection margins, 21% of the treating Korean physicians would reduce the dose of postoperative RT ≤50 Gy (based on ECOG 3311) in the tumor bed area [14, 37]. In a patient with high-risk HPV+ OPC after 2 cycles of iCHT and a PET/CT verified CR, 19% of the Korean RO specialists would indicate deintensification of the subsequent CRT [37]. In comparison to the results observed in Slovakia, a substantially higher proportion (45.7%) of the treating physicians would de-escalate primary RT in the GTVt and GTVn areas in a low-risk younger non-smoker with T1N1M0 HPV+ OPC and the exact same number (45.7%) of the specialists would do so in a low-risk elderly comorbid non-smoker with T2N1M0 HPV+ OPC. A trend towards omission of RT of the contralateral neck and omission of ipsilateral levels IB and lateral RP LNs was observed in both cases of primary RT in Slovakia. Interestingly, compared to the Korean results, only 11.4% of the Slovak RO specialists would de-escalate the dose of postoperative RT in a low-risk patient with pT1N1 M0 with R0 resection and none of the specialists would omit RT of the tumor bed. In a patient with high-risk HPV+ OPC with a CR after 3 cycles of iCHT, none of the Slovak specialists would de-escalate the dose of the subsequent RT to <60 Gy.

Although several types of deintensification strategies in the treatment of HPV+ OPC have been studied in the past few decades, none are practice-changing up-to-now and challenges remain in identifying the most suitable candidates [38]. Although the standard of care has not yet changed, there is justifiable optimism that with careful patient selection, intratreatment response assessments, and long-term follow-up, some de-escalation strategies may be feasible in the future [39].

A majority of the RO specialists involved in this questionnaire study would treat HPV+ OPC patients according to international consensus guidelines, that do not differ from HPV– OPC. However, the willingness to de-escalate the dose of primary and postoperative RT and reduce the dose of concurrent CHT in Slovakia outside of the clinical trials is high. The incorporation of standard oncological treatment deintensification into routine clinical practice will require more prospective randomized phase III trials that would confirm the exact and undoubted benefit of these treatment strategies for HPV+ OPC patients according to the rules of evidence-based medicine.

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