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A review of combined treatment strategies for HPV(+), p16(+) oropharyngeal cancer – is de-escalated radiotherapy a convincing and promising paradigm?

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Biological and clinical interest on HPV-associated oropharyngeal cancer (OPC) is rapidly increasing. The genetic and biological characteristics of HPV and p16 expression are presented. The significantly better prognosis (overall survival, locoregional control) of HPV p16(+) OPC patients has been well documented. The leading studies and clinical trials in this field are selected and discussed in details. There is a convincing suggestion that some, low-risk HPV(+) OPC patients might be overtreated. Different approaches with varying degrees of radiotherapy dose de-intensification are critically reviewed and the current de-escalated treatment paradigms are presented and discussed.

Key words: HPV-associated OPC, treatment outcome, de-escalated therapy paradigms

Introduction

Interest in an impact of the HPV status of oropharyngeal cancer (OPC) patients on optimization of therapeutic modalities and on treatment outcome has been intensively growing over the last 20 years, mainly due to the increasing incidence of the HPV(+) OPCs. Retrospective studies and several clinical trials [1–13] have already shown that HPV(+) OPC patients have significantly better locoregional control (LRC) and overall survival (OS) after standard therapeutic strategies than HPV(–) OPCs.

Although tobacco consumption has consistently diminished for over 40–50 years resulting in the decreased incidence of head and neck cancer. In contrast, the age-adjusted incidence rates of the OPCs did not fall, and in fact is continuously and dramatically rising. According to the US Cancer Statistics, HPV(+) OPCs actually comprises most of the head and neck squamous cell cancer patients [14]. Nowadays, the HPV(+) OPCs are recognized as a distant disease with a different molecular profile, radiological and clinical characteristics, and response to therapy [1, 8, 12, 14–17]. It is suggested that HPV status should be considered as a "diagnostic" marker to identify different diseases (not only in the head and neck region) rather than a "prognostic" factor within a "homogeneous" disease [14].

The ICON-S Study [18] showed that in the 7th TNM edition N classification was inadequate regarding prognosis, since there was a minimal separation in the OS among N1, N2a and N2b subsets. The ICON-S consequently proposed to reclassify them into a single N1 category, while bilateral or contralateral neck nodes should be termed as N2. In 2017, this new N classification has been adopted in the 8th TNM edition for the HPV(+) OPCs, and from that time they are recognized as a distinct and new disease [18, 19], whereas T4 or N3M0 diseases are no longer classified as stage IV [20]. Also the WHO introduced "HPV(+) OPCs" as a new disease (19).

The question whether the HPV(+) status of the OPCs might be considered as a prognostic or even a predictive marker, to optimize the treatment strategy for OPCs still remains open.

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HPV OPCs biological and clinical characteristics

The HPV carcinogenesis occurs at the basal cell layer of the oropharyngeal mucosa. It may facilitate the migration of tumour cell foci to underlying lymphatics. This may, at least partially, explain early clinical neck lymph nodes involvement, even in early stages of primary tumours [7, 8, 18].

Among over 130 different identified types of papillomaviruses, with a high risk of the oncogenic HPV p16 is associated with oropharyngeal cancer. The HPV genome consists of a non-coding long-control region, six early genes, two of which (E6 and E7) encode viral capsid proteins and facilitate viral DNA replication. The E6 oncoprotein disrupts normal apoptosis by binding and inactivating tumour suppressor p53, to promote its degradation. The E7 oncoprotein binds and degradates the RB protein. The expression of the E6 and E7 results in the inhibition of p53 – mediated apoptosis (allows the virus to replicate) and is confined to the basal layer, where the stem cells reside and cause abrogation of the cell cycle checkpoint [7, 8, 20–24].

Ang et al. [1] and Shi et al. [25] observed a strong correlation between HPV status and expression of the p16 (established as a biomarker for the function of the HPV E7 oncoprotein), suggesting that p16-expression status is likely a good surrogate for tumour HPV(+) status. This suggestion has been supported by other authors [24–28]. According to Rietbergen et al. [7, 8] epidemiologic analyses revealed the most frequent profile of HPV(+) OPC patients. They are generally younger by about 10 years, more often male, and likely have a history of tobacco and/or alcohol consumption, and have a higher number of sexual partners. The HPV(+) OPCs tend to be poorly differentiated, and mostly occur in the early tumour stage with a relatively more advanced nodal disease. It also seems that this tumour type might have a relatively low level of cancer stem cells.

Superior prognosis (locoregional control – LRC, overall survival – OS) for HPV(+) OPCs, as compared with that for the HPV(–) OPCs has been convincingly well documented in many retrospective, single arm studies and clinical trials. Higher LRC and OS among HPV p16(+) OPC patients may likely reflect higher intrinsic radio-chemosensitivity. Although response rates of the HPV p16+ OPCs to induction chemotherapy are higher than HPV p16(–) tumours [11], single agent cisplatin did not show a different impact on the elimination of occult distant metastases. Ang et al. [1, 17] and O'Sullivan et al. [2, 4] clearly documented the HPV status with respect to tobacco smoking as a major independent prognostic factor for the OPC patients, probably because these factors have an impact on the molecular profile of the cancer, and as a consequence, also on the response to therapy. Although HPV p16(+) OPCs differ from the HPV p16(–) tumours with respect to patterns of loss of heterozygosity, chromosomal abnormalities and gene-expression profiles [8, 14, 20, 22–24, 26, 29], and inversely correlate with poor prognostic markers (e.g. p13 mutations or EGFR expression), Ang [17] and Fahry [11] suggest that no specific mechanism has been found to explain directly the higher rates of response to radiation therapy and chemotherapy among patients with HPV(+) OPCs.

RT and CH-RT efficacy for HPV(+) *vs.* HPV(–) OPCs

Numerous clinical studies, including phase II–III trials, have clearly documented much higher overall survival (OC), progression free survival (PFS) and specific cause survival (SCS) of the HPV(+) OPC patients than those with HPV(-). Moreover, strong agreement HPV status with p16 expression in the OPCs was noted. Analyses performed by Ang and Sturgia [17] and Rietbergen et al. [7, 8], showed a dramatic increase in the discrimination power when OPC patients are assigned to one of the three classes (fig. 1). For

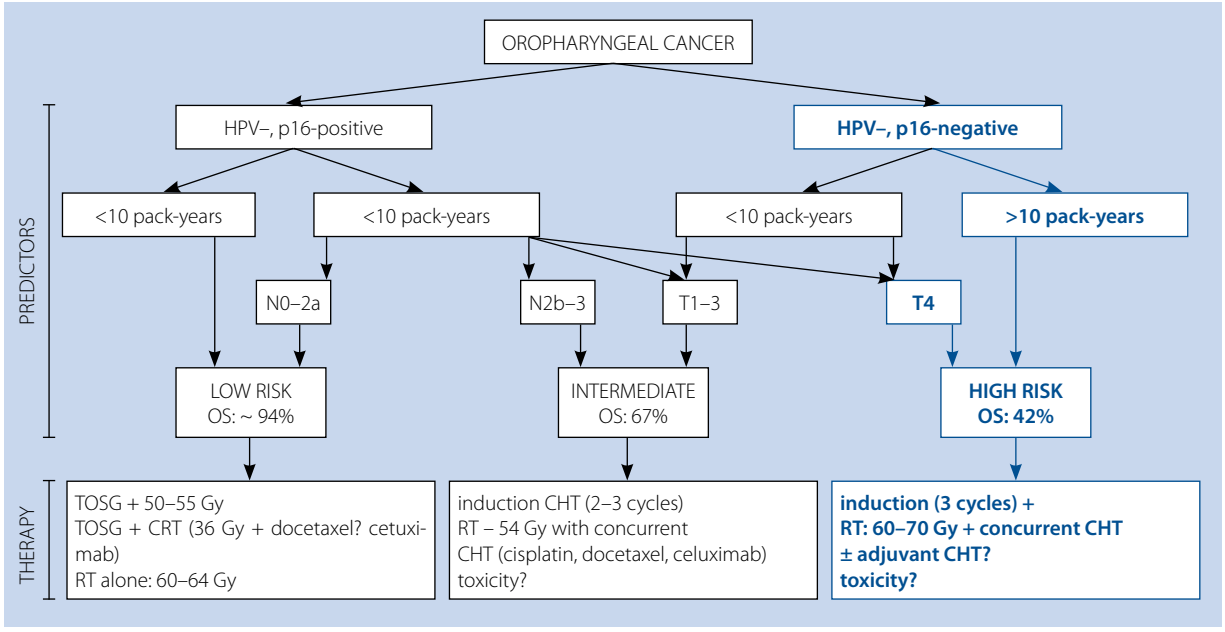

Figure 1. Overall survival of three risk subgroups of the HPV(+) OPC patients. TOSG – transoral surgery; CRT – chemoradiation; CHT – chemotherapy; OS – overall survival

class I patients, with HPV(–) and p16(–), 5-year OS ranged from 35–55%, and 59–69% for class II with HPV(–) p16(+), and 88–94% for class III with HPV(+) p16(+). According to Ang et al. dose rates of OS for the OPC patients with HPV(-) p16(+) dose to those with HPV(+) p16(+) may lead to misclassification of HPV(+) tumours as HPV(–) lesions if the OPCs status would be based on the p16 expression only. Therefore, it seems that tumours status should be expressed by an estimation of both, HPV and p16 markers.

Hong et al. [26] analyzed the impact of a combination of EGFR, HPV and p16 estimates on treatment outcome of about 270 OPC patients after radical treatment. After adjustment for age, year of diagnosis, gender, grade, T and N category and primary site within OPCs, the authors noted that the OPC patients with HPV(–)/EGFR(+) had a 13-fold higher risk of local failure and about a 4-fold higher risk of death than those with HPV(+)/EGFR(–) status. This suggests that the impact of EGFR

Table I. Review of selected studies on treatment outcomes of OPC patients depending on HPV status and treatment strategies

Study	No. cases Stage	Treatment schedules	HPV status	Outcome end-points (follow-up years)				Author(s)
				OS (%)	CSS (%)	LRC (%)	DM (%)	
RTOG 0129 (USA)	**720** OPC + LRX III–IV	72 Gy/42 fx *vs.* 70 Gy/35 fx	**HPV(+)** **HPV(–)** **risk:** low intermed high	82.4 57.1 p < 0.0001 93.5 67.0 p < 0.0001 46.2		86 65 p < 0.001	10 13 p = 0.23	Ang et al. [1, 17] (3 yrs.)
DAHANCA-6, 7 (Denmark)	**331** OPC + LRX I–IV	66–68 Gy/33–34 fx ± nimorazole (Nm)	**HPV** p16+ Nm+ Nm– **HPV** p16– Nm+ Nm–		70 63 p = 0.8 58 40 (p < 0.0001) 42 28 p = 0.02	61 35 (p < 0.001)		Lassen et al. [3] (5 yrs.)
PMH Canada (2011–2013)	**449** OPC, I–IV	60 Gy/25 fx – 70 Gy/35 fx ± cisplatin (concurr.)	**HPV(+)** RT alone CRT (cispl) **HPV(–)**	81 70 89 44	88 80 p < 0.001 93 58	93 90 p < 0.001 93 76	11 12 7 15 n.s.	O'Sullivan et al. [2, 4] (3 yrs.)
PMH Canada (2019)	**289** OPC, T1-2N1-2b	70 Gy/35 fx + cisplatin – weekly cetuximab – infrequent	**HPV(+)** r EN– r ENE+	92 68 p < 0.02		97 93 p = 0.33	5 22 p < 0.001	Billfalk-Kelly et al. [12] (2 yrs.)
UCLA (phase III) (USA)	**45** OPC, III–IV	induct. CHT (2 cycles paclitaxel + carboplatin) + 54 Gy/27 fx	**HPV(+)**			95	2	Chen et al. [5] (2 yrs.)
ECOG 1308 (phase II – USA)	**90** OPC, T1-3N0-2b	induct. CHT paclitaxel, cispl, cetuximab + 54Gy/27fx	**HPV(+)** <10 pck. tabac. >10 pck. tabac.	96 95 p = 0.04 71		78		Marur et al. [6] (3 yrs.)
Vrije Univ. Amsterdam (Denmark)	**723** OPC, II–IV	surgery + RT, RT alone CHT (various schedules)	**HPV(+)** **HPV(–)**	82.2 51.8 p < 0.0001				Rietbergen et al. [7] (3 yrs.)
TROG 02.02. (Australia)	**185** OPC + LRX II–IV	70 Gy/35 fx + Cispl 70 Gy/35 fx + tirapazamine	**HPV, p16(+)** **HPV, p16(–)**	91 74 p < 0.0001				Rischin et al. [9] (2 yrs.)
TAX 324 (USA)	**264** OPC + LRX III–IV	induct. CHT (3 cycles) docetaxol, cispl, 5-Fu + 70–75 Gy/7.5 wks.	**HPV(+)** **HPV(–)**	80 31 p < 0.0001			5 11	Posner et al. [10] (5 yrs.)
ECOG 2399 (USA)	**111** OPC + LRX II–IV	induct. CHT (2cycles) carboplatin, paclitaxel CRT – 70 Gy/7 wks. + paclitaxel	**HPV(+)** **HPV(–)**	95 62 p = 0.005				Fakhry et al. [11] (3 yrs.)

OPC – oropharyngeal cancer; LRX – laryngeal cancer; OS – overall survival; CSS – cause specific survival; LRC – locoregional control; DM – distant metastases; CHT – chemotherapy; CRT – concurrent radio-chemotherapy;, Surg – surgery; Nm – nimorazol, r ENE – radiologic extracapsular nodal extension; pck. tabac – pack-years tobacco

expression on treatment outcome might be limited to HPV(–) OPC patients, because EGFR expression was substantially greater in HPV(–) than in HPV(+) OPCs. Multimarker analyses showed that high HPV and low EGFR estimates better predict OS and CSS (cause specific survival) similar to high p16 and low EGFR. Ang et al. [1] suggest that relationships between HPV, p16 and EGFR estimates have a multifunctional character.

Tobacco smoking was found as an independent prognostic factor for OS and CSS. In the group of OPC patients the median pack-years of tobacco smoking were 12.2 for HPV(+) patients, compared with 36.5 for HPV(–) patients. Results of various studies strongly suggest that tobacco smoking likely induces additional molecular alternations in HPV-associated OPCs, that alter their biologic behavior and response to therapy.

Numerous studies, including clinical trials, on the relationship between the prognostic value of HPV and p16 status and the treatment outcome of the OPC patients are clinically heterogeneous, since they include a wide variation of T and N status and different, often combined treatment strategies. Among them, some studies with a high citation index are arbitrarily selected and presented in table I. All of these studies (fig. 2) show significantly ($p < 0.005 - p < 0.0001$) higher OS (80–95%) and LRC (61 > 90%) for HPV(+) OPCs than for HPV(–) series (31–74% and 35–75%, respectively). Some of the selected studies need detailed comments.

RTOG 0129 Trial [1, 17] and Vrije study [7]

The RTOG 0129 Trial was primarily designed to compare the efficacy of high-dose cisplatin used concurrently with either accelerated RT (72 Gy in 42 fx) or standard fractionation (70 Gy in 35 fx). Altogether, 721 H&N cancer patients with stage T2-4N0–N3 were recruited to this trial. Among the study group of 323 OPC patients (44.8%), HPV and p16 status were estimated retrospectively using stored tumour samples. Overall survival (OS) and locoregional control (LRC) end-points were evaluated. The results have shown HPV status to be the major determinant of the OS and LRC (about 20% higher for HPV(+) subset of patients than for HPV(–) ones, followed by the number of pack-years of tobacco (<10 *vs.* >10) and the nodal status (N0-2a *vs.* N2b-3) for HPV(+) tumours and tumour stage (T2–3 *vs.* T4) for HPV(–) ones. Superior prognosis for HPV(+) than HPV(-) OPCs likely reflects the higher radiosensitivity and radioresponsiveness of HPV(+) OPCs after RT combined with single agent cisplatin, but cisplatin did not differentially affect the risk of DM (10% *vs.* 13%).

The results of this study allowed the classification of OPC patients into 3 categories (fig. 1) regarding the risk of death: a low risk cohort with average 3-year OS of 93% (85 > 95%), an intermediate risk with average 3-year OS of 71% (65–75%) and a high risk cohort with average 3-year OS of about 46% (35–50%) (fig. 2). Very similar results and conclusions have been reported by Rietbergen et al. [7], who analyzed the Dutch study of HPV status in 723 OPC patients [fig. 3].

Comparing the prognostic power of the p16 vs. HPV expression in the OPCs, Ang et al. [17] noted that p16(+) correlates with a 2.2-fold higher OS than p16(–) whereas HPV(+) predicts a 1.6-fold higher OS than HPV(–). The most important observation was that OS for HPV(–) p16(+) cases was similar to the survival curve for OPC patients with both HPV(+) and p16(+). It may suggest that the prognostic value of HPV and p16 expressions should be cautiously interpreted if they are analyzed separately.

DAHANCA-6,7 Trials [3]

DAHANCA-6,7 Trials were performed (331 OPCs and LRX in stage I–IV) to test the efficacy of the hypoxic cell radiosensitizer nimorazole or placebo combined with conventionally

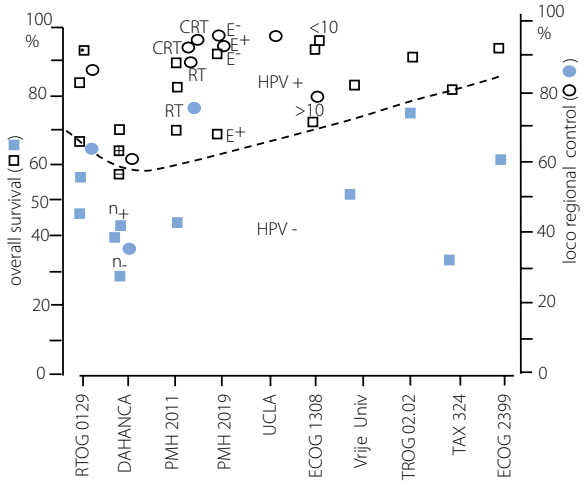

Figure 2. Scattergram of the OS and LRC reported in the various studies or clinical trials depending on the HPV status: HPV(+) – □ – low risk; ⊟ – intermediate risk; ⊞ – high risk; ⊡ – no risk estimated; HPV(–); ■, ● E (+, –) – nodal extracapsular extension; RT – radiotherapy alone; CRT – chemoradiation; <, > – pack-years tobacco; N (+, -) – nimorazole

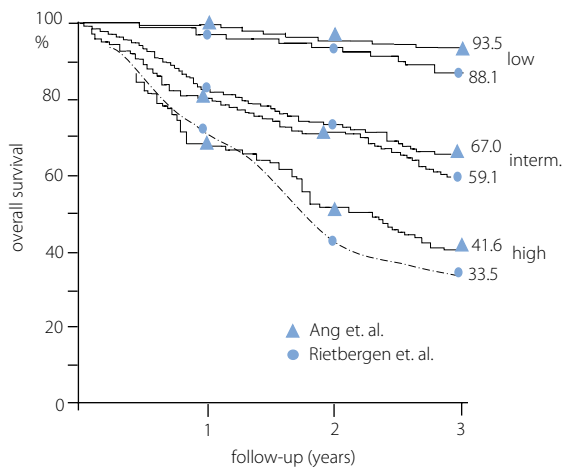

Figure 3. Algorithm of three risk subsets of the OPCs depending on HPV, p16, tobacco smoking and the respective therapy modalitied (modified from Ang et al. 1,17 and Rietbergen et al. 7).

fractionated 66-68 Gy in 33–34 fractions. The use of nimorazole significantly (p = 0.01) improved locoregional control by 14% compared to the placebo group (48% *vs.* 35%). The results of this study confirmed previous conclusions that HPV(+) p16(+) OPC patients had a significantly (p < 0.0001) superior outcome (7.5-year OS of 70% and 61% of LRC) compared with HPV(-) p16(-) patients (40% and 35% respectively). The use of nimorazole during RT significantly improved LRC compared with the placebo subgroup for p16(–) but not in the p16(+) subset. The authors suggest that the use of nimorazole can be beneficial, as long as tumours harbour hypoxic stem cells. Therefore, it might be that p16(+) tumours probably do not contain hypoxic stem cells, which would render them less resistant to RT than hypoxic tumours. Moreover, Overgaard et al. [27] have estimated plasma osteopontin level as a marker of hypoxia associated with a poor outcome after RT. They found significantly (p < 0.0001) higher concentration of osteopontin in the HPV(–) p16(–) tumours compared with about a 3-fold lower concentration in HPV(+) p16(+) tumours (41% *vs.* 16%). This findings likely support the hypothesis that HPV(+) p16(+) OPCs are less hypoxic than HPV(–) p16(–) ones, or at least, the HPV(+) OPC cells under hypoxia are approximately similarly radiosensitive as HPV(–) cells under normoxia, and it seems that hypoxic radioresistance is likely not clinically relevant in the HPV(+) p16(+) tumours.

TROG 02.02. trial

In this trial Rischin et al. [9] analyzed a prognostic power HPV p16 expression in 185 OPC patients in stage III–IV. They received RT of 70 Gy in 7 weeks with concurrent cisplatin with or without tirapazamine. The 3-year OS was significantly (p = 0.004) 17% higher in HPV(+) p16(+) group than in HPV(–) p16(–) (91% *vs.* 74%). The OS rates with/without tirapazamine were 94% *vs.* 80%, but not significant (p = 0.09), however there was a trend for improved locoregional control with tirapazamine regimen in the HPV p16(–) patients.

PMH 2011–2013 study

In this retrospective study 449 consecutive OPC patients in stage I–IV treated with RT alone were included. Four different RT regimes (70 Gy in 35 fx in 7 or 6 wks., 60 Gy in 25 fx in 5 wks. and 64 Gy in 40 fx in 4 wks.) were used. The 3-year OS in the HPV(+) subset was about 2-fold higher than in the HPV(–) subset (81% *vs.* 44%, p < 0.001). Similarly, the 3-year LRC was significantly (p < 0.001) higher for HPV(+) (93%) than that for HPV(–) (76%). The HPV(+) patients were younger, and had less tobacco (<10 pack-years), and lower alcohol consumption, and less T4 or N0 disease. Since 121 OPC HPV(+) patients with positive neck lymph nodes received concurrent chemoradiation (CRT), generally, CRT (chemoradiation) cohort had better OS than RT alone (89% *vs.*70%, p = 0.005) but similar toxicity. However, within the subset of HPV(+) patients with stage IV and minimal smokers (<10 pack-years) 3-year OS and LRC for RT alone and CRT (86% *vs.* 88% and 95% *vs.* 92%, p = 0.45–0.52) were similar but the late toxicity rate was insignificantly higher after CRT than RT alone (16% *vs.* 6%, p = 0.08). A lower OS rate in the RT-alone subset should not be entirely surprising and likely may be explained by an imbalance of several prognostic factors between the RT-alone and the CRT.

Despite very good LRC in HPV(+) patients, the DM rate did not differ much than from that for HPV(–) patients, but was slightly reduced by CRT. Although the RT-alone schedule for HPV(+), stage IV and minimal smoking patients in this study resulted in quite high OS and LCR, it consisted largely of altered, accelerated fractionation regimes. The authors suggest that the use of conventional RT-alone might be questioned and remains rather uncertain. Nonetheless, conventional or moderately accelerated RT-alone could be a reasonable option for low-risk, early stage HPV(+) patients with a minimal smoking.

TAX – 324 trial

This trial was dedicated to previously untreated OPC patients in stage III–IV and it explored the efficacy of pretty aggressive combined therapy which consisted of 3 cycles induction CHT (docetaxol, cisplatin and 5-fluorouracil) followed by RT of 70–74 Gy in 7–7.5 weeks plus concurrent weekly carboplatin with a median 5-year follow-up. The OS rate for patients with HPV(+) was about 2.5-fold higher than for those with HPV(–) (80% *vs.* 31%, p = 0.0001), but the rates of DM were not significantly different. The effects of regimes with or without taxans in patients with HPV(+) or HPV(–) did not reveal any statistical difference.

Many clinical studies, including those presently discussed, have shown unequivocally that HPV, and the p16 status of the OPCs should be considered as a major prognostic factor. However, because of the heterogeneity of other biological and clinical factors, the HPV and p16 predictors should be followed by tobacco smoking (>, < 10 pack-years), also by nodal status (N0–2a *vs.* N2b–3), and by tumour stage T2–3 for HPV(+) and T4 for HPV(–) factors.

Are HPV(+) OPCs proper candidates to dose de-escalated RT or they might be a case of "one bridge too far"?

The favourable locoregional control and overall survival of the HPV(+) OPC patients compared with the HPV(–) ones have been documented by many single-arm studies and clinical trials, however distant metastases rates are more or less the same for both [1, 2, 4, 7, 10] and seem to be the major cause of death in HPV(+) patients. On the other hand, such satisfied outcome of the HPV(+) OPC patients lead to the question of whether standard RT-doses might expose HPV(+) patients to overtreatment and to unnecessary toxic side-effects.

It seems that de-escalated treatment strategies should be proceeded with caution (23), because although the HPV status alone has occurred as an independent good prognosticator,

there is still a subset of biologically aggressive HPV(+) oropharyngeal tumours. One of the most interesting de-escalated single-arm studies was performed by Chen et al. [5]. The aim of this UCLA study (tab. I) was to investigate whether CRT with a reduced RT dose would maintain high OS while improving tolerance of the HPV(+) OPC patients. A small group of 45 HPV(+) OPCs in stage III–IV were treated with two induction cycles of paclitaxel and carboplatin. These with a complete or partial response (CR-PR), received RT after 2 weeks, with the dose reduced to 54 Gy in 27 fractions to the primary tumour, and 43 Gy to the uninvolved nodal areas. For patients with less than PR, 60 Gy in 30 fx was delivered. Acute and late toxicity was mild and grade 3 occurred in about 3–7%. At least 2-year LRC was 95%. This study shows that for the HPV(+) OPCs, stage III–IV patients RT doses could be successfully reduced by 10–15% compared with the standard doses.

A similar RT-regimen with a total dose reduced to 54 Gy in 27 fx was used by Marur et al. [6] in the ECOG 1308 phase III trial (tab. I), which consisted of 80 OPCs in stage T1–3N0–2b. The RT was preceded by 3 cycles of induction CHT (IC) with cisplatin, paclitaxel and cetuximab. The RT dose was reduced when CR or PR occurred after IC. Patients with less than PR received 69.3 Gy in 33 fx. The two-year OS was 96%, but it decreases to 71% ($p = 0.04$) in the subgroup of patients smoking more than 10 pack-years. The small sample size demands careful interpretation of these results. Nevertheless, the authors suggest that low-risk HPV(+) T1–2N0–2b OPC patients seem to be proper candidates to de-escalated RT, but not in the case of the HPV(+)/HPV(–) T3–4N2c–3 cases. This suggestion is strongly supported by O'Sullivan et al. [2, 20], Ang et al. [17] and others authors [5, 6, 14, 29, 30]. However, the relatively long overall treatment time of all therapeutic modalities (including 9 weeks of the IC) used in the ECOG 1308 trial, even with RT time reduced by 1–1.5 week, likely suggests that the net de-escalation might be close to "zero".

Chera et al. [30] carried-out a phase II NCT 0153 0997 trial of de-escalated chemoradiation for favourable-risk 45 HPV(+) p16(+) OPC patients in stage T0–T3N0–2b. Therapy consisted of 60 Gy IMRT, instead of 70 Gy and a concurrent weekly low-dose of cisplatin. The two-years OC was 98% and LRC of 87%, with evidence of decreased toxicity compared with standard therapies. The authors suggest to explore three other major approaches of dose de-escalation in HPV(+) OPCs. The first substitutes EGFR inhibitor (cetuximab) by cisplatin with the assumption of the decreased toxicity. A second approach uses transoral surgery, which is less invasive and toxic than conventional techniques, applied for early, low-risk T1–2N0–2b HPV(+) OPCs, with an IMRT dose-reduced to about 40 Gy, in case of negative margins. Finally, the third approach is limited to radiation alone, omitting chemotherapy, for HPV(+) OPC patients with stage T1-2N0-1, especially for those with <10-pack-years smoking history. Moreover Chera et al. [29] and Hong et al. [26] suggest that efficacy of cetuximab in HPV-associated OPCs might be questioned because EGFR expression in HPV(+) OPCs is lower than in HPV(–) ones, and it might be less effective than cytotoxic IC combined with RT.

Billfalk-Kelly et al. [12] have analyzed in a retrospective PMH 2019 study the impact of a radiological extracapsular nodal extension (ENE) on treatment outcome in the group of 289 T1–2N1 HPV(+) OPCs patients, based on the assumption that HPV(+) OPCs have a tendency for early nodal involvement, even in early T0-T2 tumours. The results showed significantly lower two-year OS of the r ENE(+) HPV(+) patients than for those with r ENE(–) (68% *vs.* 92%, $p < 0.02$), but there was no substantial difference in the LRC (tab. I). This study also shows that the r ENE(+) represents a subset with a significantly higher risk of distant metastases (22% *vs.* 5%, $p < 0.001$) in a population that should have an excellent prognosis. Surprisingly, in a recent study [12] of 238 stage I HPV(+) OPC patients, the authors did not find the r ENE to be a prognostic factor, but nodal status was not determined by a radiologist and the interrater reliability was not evaluated. The poor prognosis of the r ENE(+) status has been evaluated in any of RT dose-reduced studies.

An interesting small pilot study within MSKCC prospective trial IREB 04–070 [31] was focused on an assessment of pre-treatment hypoxia in the subset of 33 HPV(+) OPC patients in stage III and IVB using 18F-MISO (fluoromisonidazole) PET to select patients as candidates to de-escalated RT. 10 OPC patients (30%) had normoxic lymph nodes, and they received a total dose de-escalated by 10 Gy (from 70 Gy to 60 Gy) to the involved neck area, whereas the dose to primary tumours was 70 Gy. Twenty-six OPCs (81%) patients were hypoxic at the primary site. The 2-year OS and LRC was 100%. Overgaard [7, 27] has suggested that HPV(+) p16(+) OPC tumours probably do not contain hypoxic stem cells. Results of the pilot study of Lee [31] do not support Overgaard's suggestion, at least regarding primary tumours. In fact, the Lee' study shows that although HPV status is a valuable prognosticator, when it is used as a single factor, but it seems insufficient to guide de-escalation decision because there is still a subset of biologically aggressive HPV(+) OPCs that can recur after chemoradiation. Moreover, Sorensen et al. [32] noted that HPV(+) cells under hypoxia have approximately similar radiosensitivity as HPV(–) cells under normoxia. So, attempts at nonselective reduction either chemotherapy or radiotherapy for HPV(+) tumours should proceed carefully with caution and the use of 18F-MISO PET estimates could be an additional and helpful indicator together with other clinical factors, to identify patients who really could be candidates for de-escalation treatment modalities.

Recently, Ma et al. [33] from the Mayo Clinic (USA) made a few steps forward regarding dose de-escalated RT for HPV(+) p16(+) OPC patients. After margin-negative surgery, 80 OPC patients with ≤ 10-pack-years tobacco smoking were included into the MC1273 single arm phase II trial. Cohort A (low risk) received 30 Gy with 20 fractions of 1.5 Gy given twice-a-day over 2 weeks along with 15 mg/m^2 docetaxel on-

ce-a-week. In fact, the biological dose was even lower being 22.5 izoGy2.0 if given in 2.0 Gy fraction. Cohort B (patients with node' extracapsular extension – ECE(+)) received the same dose fractionation plus a simultaneous integrated boost to the nodal area with ECE of 36 Gy in 1.8 Gy twice-a-day fractions (biological dose = 32.4 izoGy 2.0). Overall 2-year OS for both cohorts was 98.7% and a 2-year LRC of 96.2% (100% in cohort A and 93% in cohort B). Grade 2 and 3 toxicity was generally low at 0% and 6–7% respectively. Furthermore, this study had a 33% reduction in RT costs and a 21% reduction in total treatment costs compared with standard chemoradiation. This study, like all phase II trials, requires confirmation by a phase III trials before broad applicability. Nevertheless, this aggressive de-escalation regimen (more than half of a biological standard dose of 60 Gy in 30 fractions, and shortened OTT to 2 weeks could be considered as promising and highly effective for carefully selected homogeneous subset HPV(+) p16(+) low risk OPC patients.

Summary

The HPV(+) OPCs are widely recognized as a distinct head and neck cancers. Nodal disease appears more extensive for HPV(+) OPCs at the diagnosis. The p16 can be considered a surrogate for the HPV status and the use of estimates for both HPV and p16 seems obvious. The HPV(+) p16(+) OPCs respond better to current standard therapies, including RT alone, surgery with or without adjuvant treatment, or combined chemoradiation. Consequently HPV(+) p16(+) OPC patients have a much better prognosis than those with a HPV(–) p16(–) status. The results of selected studies to the present analysis and discussion are shown in figure 2. Some of the studies suggest that smoking and some molecular deregulations, (e.g. P53 mutation and high EGFR expression) can increase the resistance of HPV(+) OPCs to therapy. Numerous available data allow to stratify OPC patients into three distinct low-, intermediate- and high-risk classes, as it has been proposed by Ang and Sturgis [17]. Their algorithm is modified and presented in figure 3 and might be a useful guide for daily clinical practice.

The general belief that low-risk HPV(+) OPCs with 3-year OS of more than 90% could be overtreated by standard therapeutic modalities has led to the concept of de-escalated treatment strategies for HPV(+) p16(+) OPCs. However actual knowledge in this field arouses some caveats and uncertainties since many studies include a relatively small number of patients, and follow-up is often too short. It seems that de-escalated strategies should be focused mainly on the low-risk HPV(+) p16(+) category of patients and consider transoral resection with or without adjuvant RT/CRT, dose-reduction in RT combined with induction chemotherapy in the group of good responders as well as reduction of RT dose to regional lymph nodes with pretreatment normoxia. For some patients with intermediate-risk and all of those with high-risk there is no room for any de-escalated treatment strategies and immunotherapy is recommended for T4N3 HPV(–) (or even HPV(+)) patients. Subsequently, large clinical trials need to be checked and actual promising observations validated, however, it seems that even well designed phase II studies might be good enough to modify treatment strategies for HPV(+) p16(+) oropharyngeal cancers. In conclusion, numerous studies the results of which are published so far convincingly show that dose de-escalation in combined treatment strategies for carefully selected HPV(+) p16(+) OPC patients offer a safe, promising and effective way across the "bridge".

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