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Original Research

Impact of cisplatin dose and smoking pack-years in human papillomavirus–positive oropharyngeal squamous cell carcinoma treated with chemoradiotherapy

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Outcome

Abstract ***Background:*** To evaluate the impact of cisplatin cumulative dose (CDDP-D) and smoking pack-years (PYs) on cause-specific survival (CSS) and overall survival (OS) in human papillomavirus–positive (HPV+) oropharyngeal carcinoma (OPSCC) using the eighth edition tumour-node-metastasis (TNM) staging classification (TNM8).

Patients and methods: We reviewed patients with HPV+ OPSCC treated with high-dose CDDP and intensity-modulated radiotherapy between 2005 and 2015 at Princess Margaret Cancer Centre. CSS and OS were compared according to CDDP-D <200/=200/>200 mg/m^2 stratified by TNM8.

Results: A total of 482 consecutive patients were evaluated (stage I/II/III: N = 189/174/119; CDDP-D <200/=200/>200 mg/m^2: N = 112/220/150). Median follow-up duration was 5.1 years (range: 0.6–12.8). Five-year CSS and OS differed by stages I/II/III: 96%/85%/88% (p=0.005) and 93%/84%/78% (p = 0.001), respectively. Five-year CSS by CDDP-D <200/=200/>200 mg/m^2 was similar in stage I (98%/95%/95%, p = 0.74) and stage II (88%/84%/

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84%, $p = 0.86$) but different in stage III (76%/98%/84%, $p = 0.02$). Five-year OS by CDDP-D <200/=200/>200 mg/m^2 did not differ significantly among stages. In the multivariable analysis, CDDP-D <200 mg/m^2 did not influence CSS in the whole cohort versus = 200/>200 mg/m^2 ($p=0.53/0.79$, respectively) but was associated with reduced CSS in stage III subgroup versus =200 mg/m^2 (=200 mg/m^2 versus < 200 mg/m^2 hazard ratio [HR] = 0.08; 95% confidence interval [CI]: 0.01–0.67; $p = 0.02$). Higher smoking PYs had no effect on CSS ($p = 0.34$) but reduced OS in the whole cohort (HR = 1.14 [95% CI: 1.02–1.27], $p=0.01$).
Conclusion: CDDP-D correlated with neither survival nor disease-specific outcomes in this large and homogeneous HPV+ cohort, although reduced CSS was observed in stageIII HPV+ OPSCC receiving CDDP-D <200 mg/m^2. Smoking PYs were negatively associated with OS but not with CSS.

1. Introduction

Human papillomavirus–positive (HPV+) oropharyngeal squamous cell carcinomas (OPSCCs) present a unique biological behaviour characterised by increased radiosensitivity and improved overall survival (OS) when compared with HPV-negative (HPV−) head and neck squamous cell carcinomas (HNSCCs) [1,2]. This disparity in prognosis was not captured in the 7th edition of American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC) tumour-node-metastasis (TNM) staging system and led the head and neck community to develop new staging criteria for HPV+ OPSCC [3]. The 8th edition TNM (TNM8) provides a more accurate prognostic classification that could lead to a better patient selection and tailored therapeutic approach in the era of de-escalation clinical trials for HPV+ OPSCC [4–7].

Concurrent chemoradiotherapy (CRT) with high-dose cisplatin (CDDP) remains the standard of care for locoregionally advanced OPSCC (LA-OPSCC) regardless of HPV status [8]. The modest survival benefit of CRT versus radiation is accompanied by significant acute and long-term toxicity that often compromises treatment tolerance, with a considerable number of patients unable to receive all 3 cycles of CDDP during standard fractionation radiotherapy [9–11]. A pooled analysis of more than 600 patients with LA-HNSCC treated at the Princess Margaret Cancer Centre in Canada and Istituto Nazionale Tumori in Italy showed that CDDP cumulative dose (CDDP-D) <200 mg/m^2 was associated with reduced OS in HPV− but not HPV+ disease with only a trend observed in patients with HPV+ OPSCC within the T4/N3 subgroup [12]. In addition, smoking pack-years (PYs) was shown to reduce OS in the HPV+ patients, consistent with other studies [13–15]. However, the end-point of OS can be confounded by the comorbid effects of long-term smoking and, as such, cause-specific survival (CSS) may be more appropriate to differentiate deaths due to cancer from tobacco-associated comorbidities and mortalities. Likely for the aforementioned reasons, smoking PYs was not included in the TNM8 classification of HPV+ OPSCC, and continued evaluation of the impact of smoking in this patient population is needed to understand its prognostic relevance.

In this study, a retrospective analysis of a large and homogeneous cohort of patients with HPV+ LA-OPSCC originally staged by TNM7 and treated with concurrent CDDP-based CRT was conducted to evaluate the impact of CDDP-D and smoking PYs on OS and CSS across TNM8 stages. In addition, the effect of smoking exposure on the risk of local, regional and distant recurrence as well as cause of death was examined.

2. Patient and methods

2.1. Study population and design

Newly diagnosed HPV+ OPSCC and carcinoma of unknown primary (CUP) with HPV+ cervical lymphadenopathy treated with concurrent high-dose CDDP-based CRT between 2005 and 2015 were identified from our in-house Anthology of Outcome Database [16]. Patient receiving other chemotherapy agents or weekly schedule were excluded. A retrospective chart review of CDDP-D and toxicity was conducted by a single rater, with 50 patients independently audited by a second rater. Concordance was 96%. Discordance was settled by consensus. HPV status was determined by p16 staining and classified as positive if there is nuclear and cytoplasmic staining in ≥70% tumour cells. In situ hybridisation to confirm the presence of high-risk HPV DNA was performed in equivocal cases. All patients were initially staged and treated according to TNM7 and re-classified by TNM8 for this study. This study was approved by the institutional research ethics board and included 283 patients from our previously reported analysis [12].

Table 1
Cohort characteristics and outcomes stratified by CDDP-D.

Variables	All patients *(N=482)*	CDDP-D (mg/m^2)			*p* value
		<200 *(N=112)*	=200 *(N=220)*	>200 *(N=150)*	
Median age (range)	57.1 (31.3, 74.4)	59.6 (40.8, 71.5)	57.5 (34.6, 74.4)	56.7 (31.3, 73.5)	**<0.001**
Gender (%)					0.074
Male	408 (85)	87 (78)	190 (86)	131 (87)	
Female	74 (15)	25 (22)	30 (14)	19 (13)	
ECOG (%)					0.51
0–1	466 (97)	109 (97)	215 (98)	142 (95)	
>/ = 2	16 (3)	3 (3)	5 (2)	8 (5)	
Smoking status (%)					0.4
Current	122 (25)	31 (28)	47 (21)	44 (29)	
Former	194 (40)	42 (38)	97 (44)	55 (37)	
Non-smokers	165 (34)	39 (35)	75 (34)	51 (34)	
Unknown	1	0	1	0	
Smoking pack-years (%)					
Median (range)	10 (0, 100)	8 (0, 80)	9 (0, 100)	10 (0, 90)	0.75
≤10 versus > 10	255 (53) versus 226 (47)	60 (54) versus 52 (46)	116 (53) versus 103 (47)	79 (53) versus 71 (47)	0.99
≤20 versus > 20	333 (69) versus 148 (31)	74 (66) versus 38 (34)	155 (71) versus 64 (29)	104 (69) versus 46 (31)	0.67
≤30 versus > 30	393 (82) versus 88 (18)	82 (73) versus 88 (27)	185 (84) versus 34 (16)	126 (84) versus 24 (16)	**0.035**
Median LDH (range)	299 (111, 502)	196 (125, 502)	204 (111, 429)	194 (128, 419)	0.42
Primary (%)					0.75
Tonsil	255 (53)	53 (47)	121 (55)	81 (54)	
Base of the tongue	189 (39)	50 (45)	83 (38)	56 (37)	
Other	9 (2)	1 (1)	5 (2)	3 (2)	
CUP	29 (6)	8 (7)	11 (5)	10 (7)	
T 8th Ed. (%)					0.91
T0-2	273 (57)	62 (55)	124 (56)	87 (58)	
T3	128 (27)	28 (25)	62 (28)	38 (25)	
T4	81 (16)	22 (20)	33 (15)	25 (17)	
N 8th Ed. (%)					0.33
N0	11 (2)	5 (4)	4 (2)	2 (1)	
N1	287 (60)	70 (62)	132 (60)	85 (57)	
N2	137 (28)	29 (26)	65 (30)	43 (29)	
N3	47 (10)	8 (7)	19 (9)	20 (13)	
TNM8 (%)					0.6
I	189 (39)	45 (40)	84 (38)	60 (40)	
II	174 (36)	39 (35)	87 (40)	48 (32)	
III	119 (25)	28 (25)	49 (22)	42 (28)	
TNM7 (%)					0.25
III	18 (4)	7 (6)	7 (3)	4 (3)	
IVA	407 (84)	92 (82)	192 (87)	123 (82)	
IVB	57 (12)	13 (12)	21 (10)	23 (15)	
RT completion-70Gy (%)					0.19
No	2 (0)	0 (0)	2 (<1)	0 (0)	
Yes	480 (100)	112 (100)	218 (99)	150 (100)	
RT break (%)					0.11
No	400 (83)	89 (79)	180 (82)	131 (77)	
Yes	82 (17)	23 (21)	40 (18)	19 (13)	
Median GTV cc (range)	21.9 (1.1, 219)	22.9 (2.8, 153)	23.9 (1.2, 151)	20.2 (1.1, 219)	0.7
CDDP-D					**<0.001**
Median (range)	200 (80, 300)	175 (80, 190)	200 (200, 200)	280 (225, 300)	
Median follow-up (range)	5.1 (0.67, 12.8)	5.5 (2.3, 11.1)	4.6 (0.6, 12.1)	5.4 (0.7, 12.8)	**0.01**
5-year OS (95% CI)	86% (82–89)	82% (75–91)	88% (83–93)	86% (80–92)	0.31
5-year CSS (95% CI)	90% (86–92)	89% (81–94)	91% (86–94)	88% (82–93)	0.66
5-year DFS (95% CI)	83% (79–86)	77% (69–85)	85% (80–90)	84% (78–90)	0.14
5-year LRC (95% CI)	96% (94–97)	97% (93–99)	97% (92–98)	93% (87–97)	0.77
5-year DC (95% CI)	89% (85–91)	87% (78–92)	89% (84–93)	90% (83–94)	0.88
5-year late toxicity (95% CI)	21% (17–25)	18% (12–27)	24% (18–31)	20% (14–28)	0.70
2-year PEG dependency (95% CI)	5% (3–7)	6% (3–13)	5% (3–9)	4% (2–9)	0.32
Cause of death (%)					0.22
Index cancer	47 (65)	12 (52)	18 (67)	17 (77)	
Other cancer	10 (14)	4 (17)	3 (11)	3 (14)	
Other cause	15 (21)	7 (31)	6 (22)	2 (9)	

Significant p values (<0.05) are highlighted in bold.
Abbreviations: TNM8 = 8th edition UICC/AJCC TNM staging criteria; TNM7 = 7th edition UICC/AJCC TNM staging criteria; CUP = cancer of unknown primary in the neck; RT = radiotherapy; GTV = gross tumour volume; CDDP-D = cisplatin cumulative dose; OS = overall survival; CSS = cause-specific survival; DFS = disease-free survival; LRC = locoregional control; DC = distant control; PEG = percutaneous endoscopic gastrostomy.

2.2. Treatment and follow-up assessment

All patients were treated with intensity-modulated radiotherapy (IMRT) to a gross tumour dose of 70 Gy in 35 fractions over 7 weeks (2 Gy/fraction). Concurrent three-weekly CDDP (100 mg/m^2) was planned on RT days 1, 22 and 43 according to institutional protocols. Local and regional recurrences were confirmed histologically, while distant metastases were diagnosed by unequivocal clinical/radiologic evidence ± histologic confirmation. Survival status was further linked to the Ontario Population-Based Cancer Registry.

2.3. Statistical analysis

For comparisons of clinical characteristics, Fisher exact test was used for categorical variables and Kruskal-Wallis test for continuous variables. Survival end-points including OS, disease-free survival (DFS), and percutaneous endoscopic gastrostomy (PEG) dependency rates were estimated using Kaplan-Meier methods. CSS (death from index cancer) was estimated using the competing risk method. Locoregional control (LRC), distant control (DC) and actuarial rate of grade 3 and 4 late toxicity according to Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group criteria were calculated by the competing risk method (considering death without an event as a competing risk). Outcome parameters were defined from date of diagnosis to date of death or last follow-up. Late toxicity and PEG dependency were calculated from date of CRT completion to date of death or last follow-up.

Clinical end-points were compared by log-rank test between CDDP-D <200, = 200 and > 200 mg/m^2 and stratified by TNM8 stage I, II and III. Cox proportional hazards regression model was used for OS, and Fine-Gray competing risk regression model was used for CSS. Multivariable analyses (MVAs) were performed to explore potential predictors for OS and CSS including CDDP-D (as >200 versus = 200 versus < 200 mg/m^2, as ≥200 versus < 200 and continuous), age (continuous), smoking PYs (>10 versus ≤ 10, as >20 versus ≤ 20, >30 versus ≤ 30 and continuous per 10) and stage. Power analyses were conducted to evaluate the association between OS and key risk factors for the entire cohort. Based on the power calculation, this study would have 86% power to identify a significant association with two-sided significance level at 0.05 and effect size (HR) of 0.7. We performed exploratory MVA to evaluate the impact of CDDP-D and smoking PYs by stage. All tests were two-sided, and results were considered significant if the pvalue was <0.05.

3. Results

3.1. Clinical characteristics

A total of 482 of 560 consecutive patients diagnosed with LA-OPSCC were eligible for the study (Fig. S1). Clinical characteristics and outcome are summarised in Table 1. Overall, patient characteristics were similar when stratified by CDDP-D. In the entire cohort, the main reasons for CDDP-D reduction/delay were myelotoxicity (38%), weight loss (20%) and ototoxicity (12%). Osteoradionecrosis was the most common late toxicity (6%) (Table S1).

3.2. Outcome stratified by stage

Median follow-up duration was 5.1 years (range: 0.6–12.8). Statistically significant differences in 5-year CSS and OS were observed by stage I, II and III ($p=0.005$ and $p<0.001$, respectively) (Fig. 1A, Table S2, Fig. S2A). While LRC remained similar across stages I, II and III ($p=0.25$), DC was significantly higher in stage I ($p=0.015$). Late toxicity and PEG dependency rate at 2 years significantly increased by stage ($p=0.005$ and $p<0.001$, respectively). Index cancer was the most frequent cause of death in the entire cohort (65%). Fifteen patients (21%) died from other causes, while nearly one-sixth of the deaths were caused by second primary malignancies (14%) (Table S2 and S3).

3.3. Impact of cisplatin dose

Five-year CSS and OS did not differ across patients receiving <200, = 200 and > 200 mg/m^2 ($p=0.66$ and $p=0.315$, respectively) in the entire cohort (Table 2, Fig. 1B, Fig. S2B). Similarly, MVA results adjusted for age, stage and smoking PYs showed that CDDP-D did not affect OS or CSS ($p = 0.35$ and $p=0.59$, respectively).

In univariable analysis, no significant differences were observed in other outcome parameters including DFS, LRC and DC. Late toxicity and PEG dependency rate at 2 years also did not differ by CDDP-D <200, = 200 and > 200 mg/m^2 ($p=0.70$ and $p=0.32$, respectively) (Table 1). Cause of death by CDDP-D was similar, although the proportion of deaths due to index cancer trended higher among patients with CDDP-D >200 mg/m^2 (52% versus 67% versus 77%, $p=0.22$).

In subgroup analysis by stage, 5-year CSS was significantly lower in patients with stage III disease receiving CDDP-D <200 mg/m^2 (76%) than in those receiving = 200 mg/m^2 (98%) and >200 mg/m^2 (84%) (p = 0.022), with a trend towards decreased 5-year OS (65% versus 89% versus 74% for <200 versus = 200

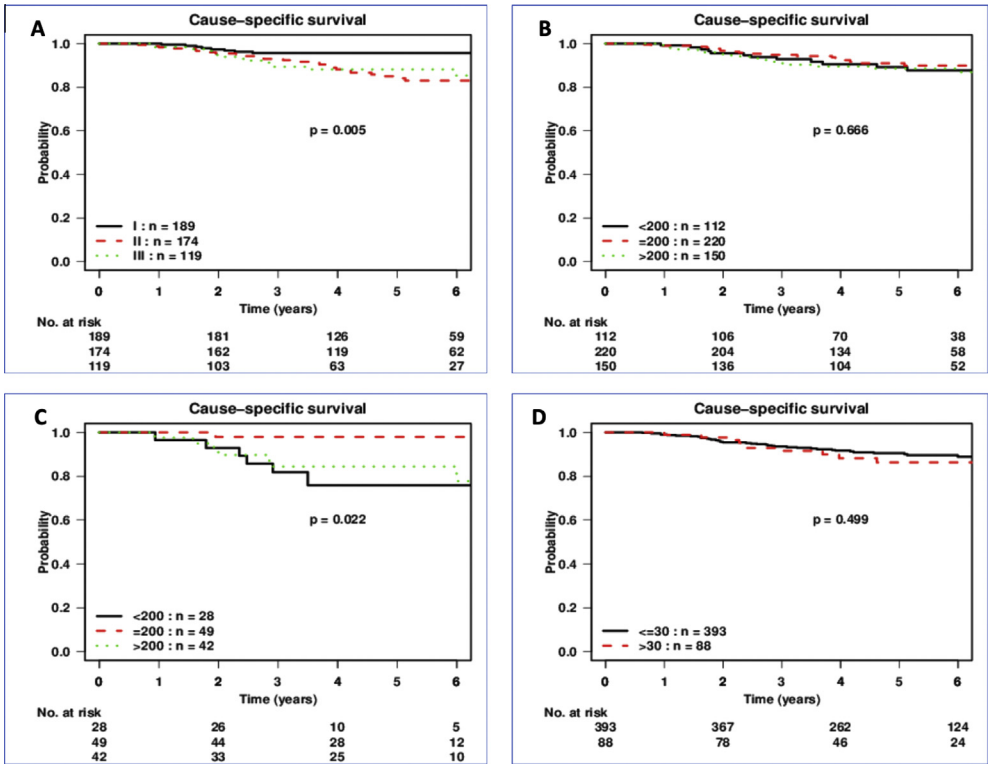

Fig. 1. Kaplan-Meier plots for 5-year CSS for (A) the entire cohort stratified by stage I, II and III; (B) the entire cohort stratified by CDDP-D (>200 versus = 200 versus < 200 mg/m^2); (C) stage III stratified by CDDP-D (>200 versus = 200 versus < 200 mg/m^2) and (D) the entire cohort stratified by smoking PYs ≤30 versus > 30. OS = overall survival; PY = pack-year; CSS = cause-specific survival.

versus > 200 mg/m^2, respectively, p = 0.09) (Table 2, Fig. 1C, Fig. S2C).

3.4. Impact of smoking pack-years

Smoking PYs partitioned at 10, 20 and 30 PYs did not impact 5-year CSS in the entire cohort or by stage (Table 2, Fig. 1D, data on 10 and 20 PYs not shown). No consistent findings were noted in MVA results for CSS when adjusted for age, stage and CDDP-D.

A significantly lower 5-year OS was observed among patients with smoking PYs >30 versus ≤ 30 (75% versus 88%, *p=0.017*) in the entire cohort regardless of stage (Table 2, Fig. S2D). In the MVA for the entire cohort adjusted for age, stage and CDDP-D, smoking PYs (continuous by 10) had a detrimental impact on OS (HR: 1.14 [95% CI: 1.02–1.27] *p=0.01*), and a similar trend was observed when using smoking PYs partitioned at 30 PYs (HR > 30 versus ≤ 30 PY: 1.59 [95% CI: 0.92–2.74], *p=0.09*). No significant correlation was seen between smoking PYs and other outcome parameters including SDS, LRC, DC or late toxicity.

4. Discussion

This single-institution, non-randomly assigned cohort study of patients with HPV+ OPSCC treated with standard-of-care CRT does not show a significant correlation between cumulative CDDP dose and survival- or disease-specific outcomes. Increased smoking pack-years is associated with reduced OS but not CSS.

An association between OS and CDDP-D has been described in few retrospective analyses involving heterogeneous patient population with LA-HNSCC treated with either definitive or postoperative CRT [17,18]. Whether the survival gain with increasing CDDP-D can be attributed to improved LRC and/or DC is unclear [12,18]. Two prospective randomised studies evaluating the role of RT plus cetuximab versus CRT as a de-escalation approach in HPV+ LA-OPSCC revealed significantly higher OS, LRC and DC in the CDDP arm regardless of stage [19,20]. However, the optimal cumulative CDDP-D and the question of whether all patients with HPV+ OPSCC needed CDDP were not addressed. The only phase III prospective study evaluating CDDP dose and schedule in LA-HNSCC indicated the relevance of these parameters in LRC although it is not fully applicable to our present study because it included mainly patients treated in the post-operative adjuvant setting with oral cavity primaries [21].

The overall impact of CDDP-D on treatment outcome and survival in patients with HPV+ LA-OPSCC remains unknown. A non-inferiority prospective comparison of two versus three cycles of CDDP-D in HPV+ disease will unlikely be pursued given the

Table 2
Impact of cisplatin dose and smoking pack-year on OS and CSS in the entire cohort and stratified by stage.

CDDP-D (mg/m^2)		Entire cohort (N = 482)	Stage (TNM8)		
			I (N = 189)	II (N = 174)	III (N = 119)
OS	**5-year OS (95% CI)**				
	<200	82% (75−91)	88% (78−100)	86% (75−98)	65% (47−89)
	=200	88% (83−93)	94% (88−99)	83% (74−92)	89% (81−99)
	>200	86% (80−92)	95% (89−100)	84% (74−96)	74% (61−89)
	p value	*0.31*	*0.13*	*0.81*	*0.09*
	MVA HR (95% CI)				
	=200 versus < 200	0.66 (0.38, 1.16 *p=0.15*)	0.57 (0.18, 1.75 *p=0.32*)	1.20 (0.49, 2.97 *p=0.69*)	0.36 (0.13, 1.03 *p=0.05*)
	>200 versus < 200	0.74 (0.41, 1.35 *p=0.33*)	0.31 (0.07, 1.34 *p=0.12*)	0.92 (0.32, 2.64 *p=0.88*)	0.91 (0.38, 2.18 *p=0.83*)
	≥200 versus < 200	0.70 (0.42, 1.15 *p=0.16*)	0.46 (0.16, 1.31 *p = 0.15*)	1.10 (0.46, 2.58 *p=0.84*)	0.61 (0.27, 1.36 *p=0.22*)
CSS	**5-year CSS (95% CI)**				
	<200	89% (81−94)	98% (84−100)	88% (70−96)	**76% (49−89)**
	=200	91% (86−94)	95% (87−98)	84% (72−90)	98% (85−100)
	>200	88% (82−93)	95% (84−98)	84% (69−92)	84% (67−93)
	p value	*0.66*	*0.74*	*0.86*	***0.02***
	MVA HR (95% CI)				
	=200 versus < 200	0.79 (0.38, 1.63 *p=0.53*)	2.59 (0.25, 26.9 *p=0.42*)	1.39 (0.52, 3.77 *p=0.51*)	**0.08 (0.01, 0.67 *p = 0.02*)**
	>200 versus < 200	1.11 (0.52, 2.34 *p=0.79*)	2.89 (0.23, 35.6 *p=0.41*)	1.03 (0.42, 4.08 *p=0.65*)	0.76 (0.2, 2.23 *p=0.62*)
	≥200 versus < 200	0.92 (0.48, 1.77 *p=0.80*)	2.71 (0.27, 26.98 *p=0.39*)	1.36 (0.53, 3.51 *p=0.52*)	0.38 (0.13, 1.07 *p = 0.066*)
Smoking PYs					
OS	**5-year OS (95% CI)**				
	≤30 versus > 30	**88% (85−92)** versus **75% (65−86)**	94% (90−98) versus 84% (71−100)	85% (80−92) versus 68% (48−97)	82% (74−91) versus 70% (54−89)
	p value	***0.01***	*0.07*	*0.29*	*0.33*
	MVA HR (95% CI)				
	Continuous per 10	**1.14 (1.02, 1.27 *p = 0.01*)**	1.18 (0.96, 1.78 *p=0.12*)	1.20 (0.97, 1.49 *p=0.1*)	1.09 (0.92, 1.29 *p=0.31*)
	≤20 versus >20	1.39 (0.85, 2.26 *p=0.19*)	1.65 (0.61, 4.46 *p=0.33*)	1.41 (0.62, 3.21 *p=0.41*)	1.19 (0.56, 2.56 *p=0.65*)
	≤30 versus > 30	1.59 (0.92, 2.74 *p=0.09*)	2.31 (0.77, 6.9 *p=0.13*)	1.66 (0.32, 2.84 *p=0.32*)	1.26 (0.57−2.79 *p=0.57*)
CSS	**5-year CSS (95% CI)**				
	≤30 versus >30	90% (87−93) versus 86% (75−92)	97% (92−99) versus 90% (71−97)	87% (80−92) versus 68% (30−86)	86% (76−92) versus 94 (75−98)
	p value	*0.49*	*0.11*	*0.14*	*0.20*
	MVA HR (95% CI)				
	Continuous per 10	1.08 (0.92, 1.26 *p=0.34*)	1.27 (0.86, 1.88 *p=0.23*)	**1.27 (1.01, 1.58 *p = 0.03*)**	0.84 (0.66, 1.06 *p=0.14*)
	≤20 versus >20	1.26 (0.67, 2.37 *p=0.47*)	1.39 (0.33, 5.81 *p=0.65*)	1.78 (0.78, 4.05 *p=0.17*)	0.66 (0.23, 1.90 *p=0.45*)
	≤30 versus > 30	1.27 (0.58, 2.78 *p=0.55*)	3.48 (0.79, 15.33 *p=0.09*)	2.25 (0.77, 6.59 *p=0.14*)	0.29 (0.07, 1.19 *p=0.08*)

Abbreviations: MVA = multivariable analysis; TNM8 = 8th edition UICC/AJCC TNM staging criteria; CDDP-D = cisplatin cumulative dose; PYs = pack-years; OS = overall survival; CSS = cause-specific survival; HR = hazard ratio.
Note: MVA for OS was adjusted for age, stage and smoking PYs. MVA for CSS was adjusted for stage and smoking PYs. MVA for TNM8 subgroups includes CDDP-D and smoking PYs.
Note: Significant *p*-values are in bold.

number of patients required; hence, our report represents the largest retrospective cohort specifically interrogating this question.

In our previous retrospective study including more than 600 patients with HNSCC treated with primary CRT, we found no significant correlation between CDDP-D and OS or other disease-control outcomes in the HPV+ subgroup [12]. The current analysis involved a larger, homogeneous cohort of patients with HPV + LA-OPSCC uniformly treated with IMRT which excluded patients treated with weekly CDDP and other chemotherapy agents. CDDP-D (<200 mg/m^2, = 200 mg/m^2 or >200 mg/m^2) had no significant effect on 5-year OS, 5-year CSS or any of the other outcome parameters including DFS, LRC and DC in the entire cohort, but the present study is underpowered for effect sizes of HR < 0.7. In the exploratory subgroup MVA by stage, CDDP-D <200 mg/m^2 was associated with reduced CSS in patients with stage III disease despite no decrease in either LRC and/or DC was observed. Overall, CSS remained poor in stage III subgroup regardless of CDDP-D, mainly because of reduced DC. These results suggest that the therapeutic benefit of standard-of-care CRT might have reached a plateau and support the need for chemo-additive strategies in stage III HPV+ OPSCC such as immunotherapy-based CRT approaches being explored in ongoing clinical trials (*NCT02952586, NCT03040999*). Data on de-intensification are not yet mature to support de-escalation strategies outside of prospective clinical trials.

We additionally analysed the impact of smoking in our cohort as its role as a prognostic biomarker for risk stratification in HPV+ disease remains controversial [1,22]. In retrospective analyses of heterogeneous cohorts of patients with LA-OPSCC treated with different treatment modalities, smoking negatively impacted OS and DC, while other studies failed to show a correlation with CSS and disease-control outcomes in HPV+ patients [13,15,23,24]. In more than 200 patients with TNM8 I to III HPV+ OPSCC treated with RT or CRT, smoking status and smoking PYs partitioned at either >10 or ≥20 were strong negative prognostic factors in the MVA for OS and DFS and were significantly correlated with lower LRC and DC, but the effect on CSS was not evaluated [14]. In our study, neither smoking status nor PY (continuous by 10 or partitioned at 10, 20 and 30 PYs) impacted 5-year CSS or any disease-specific outcome parameter (DFS, LRC and DC). However, smoking PY (continuous by 10) was found to be an independent negative prognostic factor in the MVA analysis for OS, and >30 PYs smoking history was significantly associated with lower 5-year OS. The majority of the patients in our cohort had a history of smoking, with a quarter of them being active smokers at the time of diagnosis, similar to previous studies involving HPV+ patients [14,15]. The distribution of the smoking variables was also similar across stage and CDDP-D subgroups, therefore minimising their potential confounding effect. Our data on the differential impact of smoking history on 5-year CSS and OS raise the importance of considering both parameters as efficacy end-points. Smoking has a direct impact on overall health, and comorbidities are associated with decreased survival in HNSCC regardless of treatment intervention and stage [25]. Among patients with HNSCC, smokers are at higher risk of developing secondary malignancies, especially younger patients who more frequently present with HPV+ disease [26,27]. In our study, 14% of the deaths were caused by second malignancies including lung, oesophagus and head and neck, commonly smoking-related cancers. This percentage remained similar across stage and CDDP-D subgroups and might explain the differential impact of smoking on OS and CSS. Smoking affects RT efficacy and toxicity, which may ultimately affect CSS [28,29]. Despite the well-known implications of smoking in carcinogenesis and immunosuppression, the role that tobacco plays in the biology of HPV+ OPSCC has not yet been elucidated and the few retrospective studies comparing the genomic and immune landscapes of HPV+ tumours in smokers versus non-smokers have shown inconsistent results [30–32].

Despite the large, selected and homogeneously treated patients evaluated, we acknowledge the limitations inherent to the retrospective nature of this study. While the oncologic outcomes were recorded prospectively, CDDP-D and toxicity rates were collected retrospectively and potential confounders, including patient compliance, social and economic factors, were unavailable. Although cause of death was prospectively attributed based on death certificate and treating clinician's interpretation, mis-attribution could not be entirely excluded because of the challenges in determining underlying cause of death in a few cases. The study was underpowered to detect differences in specific subsets given the small sample size in some subgroups.

The authors believe that the results of this study are of particular relevance for current practice and may contribute to guiding risk stratification and new treatment strategies within clinical trials. While awaiting prospective data, CRT should remain the standard of care in this patient population, although treatment intensification approaches should be pursued when available for patients with stage III disease. Smoking was correlated with patients' OS but not CSS or disease-control outcomes in HPV+ disease; hence, its role in risk stratification and treatment selection should be investigated in prospective studies.

Conflict of interest statement

A.S. has served the role of a consultant for Merck (compensated), Bristol-Myers Squibb (compensated),

Novartis (compensated) and Oncorus (compensated) and has receivedgrant/research support from (clinical trials) Novartis, Bristol-Myers Squibb, Symphogen AstraZeneca / Medimmune, Merck, Bayer, Surface Oncology, Northern Biologics, Janssen Oncology / Johnson & Johnson, Roche and Array Biopharma. L.L.S. has served the role of a consultant for Merck (compensated), Pfizer (compensated), Celgene (compensated), AstraZeneca/Medimmune (compensated), Morphosys (compensated), Roche (compensated), GeneSeeq (compensated), Loxo (compensated), Oncorus (compensated) and Symphogen (compensated); has received grant/research support from (clinical trials) Novartis, Bristol-Myers Squibb, Pfizer, Boerhinger-Ingelheim, Regeneron, GlaxoSmithKline, Roche / Genentech, Karyopharm, AstraZeneca / Medimmune, Merck, Celgene, Astellas, Bayer, Abbvie, Amgen, Symphogen and Intensity Therapeutics; and is a stockholder in Agios (spouse). All remaining authors have declared no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.06.019.

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