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Oropharynx Squamous Cell Carcinoma-Management Outcomes Over Time

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ABSTRACT

Introduction: Oropharyngeal squamous cell carcinoma has changed over the last few decades. This review will highlight these changes, utilising data amassed over many years from a single centre.

Methods: This Ethics approved study defines three Human Papillomavirus (HPV) patient populations: HPV not tested (HPVU), representing earlier treated patients, HPV tested and negative (HPVN), and HPV tested and positive (HPVP). Eligible patients include definitive treatment at the Prince of Wales Hospital, squamous cell carcinoma histology, age ≥ 18 years, origin in the oropharynx, and a minimum two years follow-up. Endpoints were local and ultimate local control (ULC), nodal and ultimate nodal control, and overall and Cancer-Specific Survival (CSS). Analysis was performed using the Kaplan-Meier method and log-rank test to describe time-to-event data.

Results: There were 600 eligible patients: 409 HPVU, 51 HPVN, and 140 HPVP. ULC was 75% for HPVU, 90% for HPVN, and 91% for HPVP. CSS was superior for HPVP group, however, the patient groups were different, with the HPVP group more likely to be younger, a non-smoker, good performance score, with less local disease, and more nodal disease. Nodal sites of involvement were comparable across all the three groups. Over 90% of all episodes of treatment failure occurred at the initial site of disease. HPVP patients did not have an increased risk of developing another malignancy, compared to the other two groups.

Conclusion: It is well accepted that the HPVP patient has different disease with a better outcome, this review addresses these differences.

Keywords: Carcinoma; Squamous Cell; Head and neck neoplasm; human papillomavirus; Local control; Oropharynx; Survival

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INTRODUCTION

Head and Neck Cancers (HNC), particularly those of squamous Cell Carcinoma (SCC) origin, remain a world-wide problem. [1,2] With a decline in tobacco usage internationally, there is a decline in the incidence of many cancers. [3] Of importance was the recognition that a different group of patients with an oropharyngeal carcinoma was emerging from the late 1990's. [4] These patients were younger men of whom many were non-smokers, as it became apparent that human papillomavirus (HPV) was the causative agent, [5] and that this "new" disease was different. [6,7] Patient demographics were different to smoking related oropharyngeal carcinoma [8], more typically there was bulky nodal disease, [9] greater sensitivity [10,11] to treatment, and the outcomes were better. [12] This was not absolute, smokers who had HPV positive (HPVP) disease had better results than HPV negative (HPVN) patients, however, not to the same extent. [13-15] There was also concern that elderly HPVP patients may not do as well as younger HPVP patients. [16]

Surgery, with appropriate reconstruction, has previously been a commonly used treatment for HPV unknown (HPVU) and HPVN. [17] Resections over the last 20 years have used microscopically guided laser surgery, [18] with more recently Transoral Robotic Surgery (TORS). [19,20] Consideration of which mode is not only influenced by cancer outcome, [17] but also subsequent function [21] and cost-effectiveness. [22,23] Similarly, radiotherapy has evolved with different treatment approaches (e.g., Intensity Modulated Radiotherapy-IMRT), exploration of different fractionated methods, [24-26] and the use of concurrent chemotherapy. [27,28] Modern imaging approaches utilising functional imaging (positron emission tomography-PET) has resulted in stage shift for many patients and reducing the number of post-chemoradiotherapy neck dissections. [29,30] The impact of this on Overall Survival (OS) remains to be established. [31] De-intensification of treatment is also being pursued. [32,33]

Whilst current treatments are different, to establish the best treatment, comparisons are required. It is not just treatment that needs to be considered for comparison, are the patients and the disease also changing at the same time? The aim of this review is to evaluate-three patient populations (HPVU, HPVP, HPVN), addressing patient, disease, and treatment characteristics, to quantify the nature and extent of outcomes.

MATERIALS AND METHODS

This is an ethics approved (South Eastern Sydney Local Health District 10/040) retrospective study of prospectively collected data with patients presenting and being treated from 25/05/1970-19/12/2018. Patients included in this study provided written informed consent at the time of the initial consultation. Eligible patients met the following criteria: managed at the Prince of Wales Cancer Centre (POWCC), histology of SCC, origin in the oropharynx, aged ≥ 18 years, with minimum two-year follow-up. Excluded were patients with recurrent/progressive disease (treated elsewhere), or had distant disease at presentation. All staging was via the 2009 Union for International Cancer Control (UICC) 7th Edition manual.

Patient data for this audit is in the POWCC Head and Neck Cancer (POWHN) database, anatomically site orientated with data allocated to three categories: patient, disease, and treatment information, with subsequent outcome data. This included clinical notes, imaging reports, pathology, and practitioner correspondence.

Routine follow-up after treatment was usually at three-four month intervals during the first two years, four-six months into five years, and then 12-monthly. PET imaging was not a routine investigation during the timeframe of this audit. Follow-up information addressing disease status (disease-free or recurrent/progression) was sought. Death information was obtained from the NSW Registry of Births, Deaths and Marriages, and the National Death Index Database (EO2017/5/392).

Treatment

An active Multidisciplinary Team (MDT) for the head and neck clinic has existed for the full duration of this study, with discussion of management decisions defining the resulting treatment. MDT members were/are experienced head and neck respective and reconstructive surgeons, medical and radiation oncologists, imaging specialists, and allied health staff.

Radiotherapy with appropriate head-fixation was delivered five days per week, all fields treated with 2-2.5 gray (Gy) per fraction, progressively moving from 2D to 3D planning, and more recently, IMRT. Concurrent chemotherapy was typically three-weekly high dose or weekly low dose Cisplatin.

Nodal sites were addressed as required by the clinical situation including standard prophylactic sites. HPVU and HPVN palpable nodal sites were usually addressed surgically.

Post-surgical radiotherapy (± chemotherapy) was dictated by margins, extent of nodal disease, and extracapsular nodal status. As HPV status became an important determinate of management, and with robotic surgery more recently available, a policy of non-surgical treatment for HPVP disease dominated.

Patient factors were a strong defining feature in management decisions, scored by modified Charleson Comorbidity Indices.

Outcome

All outcomes were measured from the initial date of treatment. The primary endpoint was time to local failure, defined as persistent disease within the Oropharynx (OP) after treatment, or a local recurrence after a complete response (e.g. macroscopically complete resection). Ultimate local failure was declared when there was a local failure and salvaged treatment was not performed, or salvage treatment was performed, however, the cancer recurred. Similar criteria were applied to nodal and ultimate nodal failure.

Cancer-Specific Survival (CSS) was the secondary endpoint, defined as survival or death in patients without HNC (no primary and/or regional recurrence and/or distant disease). Overall Survival (OS) recorded the subsequent fate of the patient without defining the cause of death.

The tertiary endpoint was development of another malignancy unrelated to the defined OP carcinoma.

Statistical evaluation

Statistical analysis was performed using SPSS Statistics 26.0 (IBM, Armonk, New York). The Shapiro-Wilk test determined data distribution for continuous variables. The mean (range) and median (Interquartile Range (IQR)) values were reported for normally and non-normally distributed data respectively. Categorical variables were reported as frequencies and analysed using Pearson Chi-square or Fisher's Exact Test. Normally distributed

continuous variables were analysed using one-way ANOVA and Kruskal-Wallis test for non-normally distributed continuous variables.

Time-to-event analysis was performed using the Kaplan-Meier method. The log-rank test assessed differences between curve, the Mann-Whitney U test highlighted differences between two groups, for all groups. The level of significance for all tests was $P<0.05$ and all P-values are two-sided.

RESULTS

There were 943 patients entered into the OP component of the POWHN database, of which 600 patients were eligible for evaluation. Four-hundred patients were untested for HPV, nine were tested but no result was available, thus there were 409 unknowns. There were 140 who tested as positive, and 51 as negative.

Patient characteristics

The patient demographics are listed in Table 1. HPVP patients were more likely to be younger ($p<0.001$), male ($p=0.002$), have operable cancer ($p=0.003$), fitter with a lower ECOG performance score ($p<0.001$), and were less likely to be smokers ($p<0.001$) or have a prior head and neck malignancy ($p=0.002$). This defines a very different prognostic group which needs to be considered when addressing outcomes.

Disease characteristics

Lateral pharyngeal wall involvement was more common in HPVN patients (Table 1) compared to the other two groups ($p<0.001$), with HPVP patients more likely to have a poorly differentiated carcinoma ($p<0.001$). HPVN and HPVU were more likely to have N0 disease ($p<0.001$), whereas HPVP patients were more likely to have N2-3 disease. Nodal sites of disease are indicated in Figure 1 with no difference in sites of nodal involvement between the three groups. HPVP patients were more likely to have stage III-IV disease ($p<0.001$), more typically a factor conveying a worse outcome.

Treatment characteristics

No HPVP patient in this series had surgery only, with small proportions in the other two groups (Table 2). In the HPVU group, 43% had radiotherapy only, with a median dose of 65 Gy in 33 fractions over 43 days, with 24 patients (7%) having a treatment interruption of greater than one week. Ninety-one (22%) patients had surgery and radiotherapy with a median post-operative dose of 60 Gy in 30 fractions over 42 days, and only four patients with a treatment interruption of greater than one week. The HPVN group had comparable treatment to the HPVU patients, although a lower likelihood of chemoradiotherapy, and more likely to have surgery plus adjuvant radiotherapy.

In the HPVP group, 27 patients (19%) had surgery and post-operative radiotherapy, 26 (19%) had radiotherapy only (more typically for early stage disease) and 81 (58%) had chemoradiotherapy. The regimen typically used in this situation was a dose of 68 Gy (in 34 fractions) in an accelerated BD boost approach over a median duration of 40 days, with weekly low dose Cisplatin for a minimum of five courses.

The type of surgical procedure to the primary and reconstruction utilised is indicated in Table 2. Tongue resections were frequently used in HPVU patients (n=47, 37%). Primary closure was infrequent in all three groups, local rotational flap and microvascular free flaps were the more likely means of reconstruction.

In the HPVU group, 125 patients had surgery to the primary site, close margins in 39 (31%) patients, positive in 30 (24%), and negative in 45 (36%). Similar patterns in close and positive margins were seen in the other two groups (Table 2). Regarding neck dissection pathology, one patient in the HPVP group was pathologically negative, reflecting the greater likelihood of more significant neck disease, and greater use of non-surgical treatment.

Treatment outcome

There was a higher likelihood of HPVP patients achieving a complete response (97%) versus the HPVN (84%) or HPVU patients (85%) (Table 3, p=0.009). For HPVP patients, local recurrence/progressive disease occurred in 13 patients (9%). The HPVN group had a local recurrence figure of 7 (14%) and a progressive disease figure of 5 (10%), a combined figure of 12 (24%) (Figure 2a, p<0.001). A comparable trend was evident in the HPVU group with progression in 51 (12%) and local recurrence in 62 (15%), for a combined figure of 113 (28%). The median times to local recurrence were 7.3 months, 6.7 months and 6.7 months respectively. Over 90% of all episodes of treatment failure occurred at the initial treatment site (Table 3).

Ultimate local control was achieved in 128 (91%) patients who were HPVP, 46 (90%) of the HPVN group and in 308 (75%) of the HPVU group, after initial and salvage treatments were considered (Table 4, Figure 2b, p<0.001). For patients treated with radiotherapy ± chemotherapy, ultimate local control was achieved in 101 (94%) HPVP patients, 17 (90%) HPVN patients, and 185 (72%) HPVU patients (Figure 2c). Contrastingly, 27 (82%) HPVP patients, 29 (91%) HPVN patients, and 122 (86%) HPVU patients treated with surgery ± radiotherapy achieved ultimate local control (Figure 2d). When controlled by treatment, those having radiotherapy as the main treatment had a superior outcome (p<0.001), a likely reflection of HPV status. Whereas for surgery as the main treatment, there was no difference in outcomes for HPVN and HPVU patients (p=0.847).

Nodal failure was a less likely event with 17 (12%), 11 (22%), and 78 (19%) for the HPVP, HPVN and HPVU groups respectively (figure 2e), comparable across subgroups (p=0.115). The median time to nodal failure was longer in the HPVP group (14 months, p=0.021. There were significantly more (p=0.004) nodal failures in the HPVP population treated bilaterally (15/83, 18%) compared to patients treated unilaterally (1/55, 2%), potentially reflecting greater bulk of disease in bilaterally treated patients. Ultimate nodal control occurred in 131 (94%) of the HPVP group, 42 (82%) of the HPVN patients, and in 342 (84%) in the HPVU group. Distant metastatic disease as the site of failure was present in 15 HPVP patients (11%), 8 (16%) in HPVN and 42 (10%) in HPVU groups, with the lungs being the main site.

HPV status was associated with CSS (Figure 3a, p=0.007) and OS (Figure 3b, p<0.001). HPVP patients had better survival than HPVN and HPVU patients, with no observed difference in survival between HPVN and HPVU patients. Treatment time effect is well defined in the HPVU group, where patients experiencing a treatment interruption of greater than one week had a statistically significant lower local (and ultimate local) control (Figure 4) and CSS rate.

In terms of the tertiary endpoint, the HPVP patient is less likely to develop a second malignancy (Figure 3c). As a potential consequence of longer follow-up time, 30% (n=122/409) of HPVU patients developed a subsequent malignancy with 64 (53%) being another HNC and 28 (23%) a lung cancer.

There was no statistically different outcome with the HPVP population between current smokers and non-smokers, for initial local control (Figure 5a, p=0.982) and ultimate local control (Figure 5b, p=0.827) following salvage treatment. There was no difference in outcome within the HPVP patients between those aged <65 years versus those aged >65 years (Figure 5c, p=0.115). Within the HPVU patients, treatment before 1990 was no different in outcome to those treated after 1990 (Figure 5d, p=0.204).

Table 1: Patient demographics and tumour features

	HPVP (n=140)	**HPVN (n=51)**	**HPVU† (n=409)**	**p-value**
Age at presentation, years, mean (range)	57 (31-85)	63 (41-82)	61 (27-90)	**<0.001**§
Gender				
Male	124 (89%)	34 (67%)	323 (79%)	**0.002**
Female	16 (11%)	17 (33%)	86 (21%)	
Previous tumour¶				
Head and neck	5 (4%)	3 (6%)	56 (14%)	**0.002**
Lung	0	1 (2%)	3 (1%)	0.225‡
Other	15 (11%)	7 (14%)	26 (6%)	0.069‡
Comorbidities¶				
Diabetes	15 (11%)	4 (8%)	19 (5%)	**0.036**
Hypertension	43 (31%)	17 (33%)	84 (21%)	**0.014**
Hypothyroidism	1 (1%)	0	6 (2%)	0.831‡
Tobacco use				
Never smoked	31 (22%)	0	44 (11%)	**<0.001**
Ex-smoker, not for two years	63 (45%)	13 (25%)	98 (24%)	
Current or recent smoker	44 (32%)	37 (73%)	253 (62%)	
Unknown	2 (1%)	1 (2%)	14 (3%)	
Alcohol consumption				
Nil	22 (16%)	13 (25%)	56 (14%)	**0.002**
Social only	42 (30%)	4 (8%)	79 (19%)	
Daily drinker	74 (53%)	31 (61%)	245 (60%)	
Unknown	2 (1%)	3 (6%)	29 (7%)	
Cancer operable	128 (91%)	47 (92%)	330 (81%)	**0.003**
Fit for operation	137 (98%)	49 (96%)	381 (93%)	0.095
Performance (ECOG) status				
0 - Normal	93 (67%)	28 (55%)	137 (33%)	**<0.001**‡
1 - Symptoms/self-care	42 (30%)	19 (37%)	213 (52%)	
2 - Ambulatory <50%	2 (1%)	3 (6%)	11 (3%)	
3 - Ambulatory >50%	0	0	2 (1%)	
4 - Bedridden	1 (1%)	0	0	
Unknown	2 (1%)	1 (2%)	46 (11%)	
Site				
Anterior wall	48 (34%)	5 (10%)	157 (38%)	**<0.001**‡
Lateral wall	89 (64%)	41 (80%)	165 (40%)	
Posterior wall	0	1 (2%)	20 (5%)	
Superior wall	1 (1%)	4 (8%)	67 (17%)	
Unknown	2 (1%)	0	0	
Tumour grade				

Well differentiated	2 (1%)	3 (6%)	44 (11%)	**<0.001**
Moderately well differentiated	27 (19%)	30 (59%)	186 (45%)	
Poorly differentiated	67 (48%)	13 (25%)	96 (24%)	
Unknown	44 (32%)	5 (10%)	83 (20%)	
T stage (7th edition)				
T1	51 (36%)	6 (12%)	82 (20%)	**<0.001**
T2	46 (33%)	14 (27%)	154 (38%)	
T3	35 (25%)	26 (51%)	152 (37%)	
T4	8 (6%)	5 (10%)	21 (5%)	
N stage (7th edition)				
N0	18 (13%)	22 (43%)	182 (44%)	**<0.001**
N1	31 (22%)	9 (18%)	86 (21%)	
N2	82 (59%)	14 (27%)	121 (30%)	
N3	9 (6%)	6 (12%)	20 (5%)	
Overall stage (7th edition)				
I	3 (2%)	4 (8%)	45 (11%)	**<0.001**
II	8 (6%)	9 (18%)	80 (20%)	
III	33 (23%)	16 (31%)	131 (32%)	
IV	96 (69%)	22 (43%)	153 (37%)	

ECOG: Eastern Cooperative Oncology Group; HPVN: Human Papillomavirus Negative: HPVP: Human Papillomavirus Positive; HPVU: Human Papillomavirus Unknown.

†Includes 9 patients with unknown p16 status following testing.

‡Fisher's Exact Test, bold values indicate statistical significance, 2-sided $p<0.05$, replaces Pearson Chi-square as default test when ≥20% of cells have an expected count less than five.

§One-way ANOVA (Tukey HSD), bold values indicate statistical significance, 2-sided $p<0.05$, used to compare the mean for multiple groups.

¶Not mutually exclusive, patients may have multiple previous tumours or comorbidities.

Table 2: Treatment details.

	HPVP (n=140)	**HPVN (n=51)**	**HPVU† (n=409)**	**p-value**
Treatment modality				
Surgery	0	9 (18%)	45 (11%)	**<0.001**‡
Radiotherapy	26 (19%)	15 (29%)	175 (43%)	
Chemoradiotherapy	81 (58%)	4 (8%)	82 (20%)	
Surgery plus adjuvant radiotherapy¶	27 (19%)	20 (39%)	91 (22%)	
Surgery plus chemoradiotherapy	6 (4%)	3 (6%)	6 (2%)	
Chemotherapy	0	0	10 (2%)	
Conventional radiotherapy details (± surgery ± chemotherapy)ǁ	**140**	**42**	**354**	
Dose, gray, median (IQR)	68 (66-68)	64 (58-68)	65 (60-68)	**<0.001**§
Fractions, median (IQR)	34 (33-34)	33 (30-34)	33 (30-34)	**<0.001**§
Treatment length, days, median (IQR)	40 (39-42)	41 (38-44)	43 (40-47)	**<0.001**§
Treatment interruptions >1 week	1 (1%)	0	24 (7%)	**0.005**
Conventional radiotherapy details (radiotherapy only)	**26**	**15**	**175**	
Dose, gray, median (IQR)	68 (68-68)	68 (66-68)	66 (64-68)	**0.004**§
Fractions, median (IQR)	34 (34-34)	34 (33-34)	33 (32-34)	0.086§
Treatment length, days, median (IQR)	41 (39-43)	43 (40-44)	44 (41-48)	**0.017**§
Treatment interruptions >1 week	0	0	13 (8%)	0.326‡

Conventional radiotherapy details (surgery plus adjuvant radiotherapy ± chemoradiotherapy)	**33**	**23**	**97**	
Dose, gray, median (IQR)	62 (60-68)	60 (56-62)	60 (56-65)	**0.005**[§]
Fractions, median (IQR)	32 (30-34)	31 (28-31)	30 (28-33)	**0.017**[§]
Treatment length, days, median (IQR)	40 (38-42)	40 (37-43)	42 (38-45)	0.202[§]
Treatment interruptions >1 week	0	0	4 (4%)	0.618[‡]
Brachytherapy details (± surgery)[‖]	**0**	**0**	**10**	
Dose, gray, median (IQR)	0	0	30 (25-60)	NC
Depth, mm, median (IQR)	0	0	5 (5-9)	NC
Treatment length, days, median (IQR)	0	0	3 (3-5)	NC
Surgical treatment (± radiotherapy ± chemotherapy)	**33**	**32**	**142**	
Surgery to primary site	29 (88%)	31 (97%)	125 (88%)	0.392[‡]
Neck dissection only	4 (12%)	1 (3%)	17 (12%)	
Neck dissection	**33**	**32**	**142**	
None	9 (27%)	5 (16%)	52 (37%)	0.271[‡]
Limited	4 (12%)	5 (16%)	21 (15%)	
Unilateral	19 (58%)	21 (65%)	59 (41%)	
Bilateral	1 (3%)	1 (3%)	9 (6%)	
Unknown	0	0	1 (1%)	
Neck dissection pathology	**24**	**27**	**89**	
No tumour found	1 (4%)	12 (45%)	33 (37%)	**0.004**[‡]
Intracapsular	13 (54%)	10 (37%)	32 (36%)	
Focal (extracapsular extension)	9 (38%)	2 (7%)	14 (16%)	
Gross (extracapsular extension)	0	1 (4%)	8 (9%)	
Tumour present, unknown extent	0	0	1 (1%)	
Unknown	1 (4%)	2 (7%)	1 (1%)	
Tumour margins for primary	**29**	**31**	**125**	
Negative	6 (21%)	8 (25%)	45 (36%)	0.278[‡]
In situ	0	1 (3%)	7 (6%)	
Within 5mm	9 (31%)	11 (36%)	39 (31%)	
Positive	14 (48%)	11 (36%)	30 (24%)	
Unknown	0	0	4 (3%)	
Perineural extension from primary	**29**	**31**	**125**	
Absent	28 (97%)	20 (65%)	113 (91%)	**0.002**[‡]
Present	1 (3%)	10 (32%)	9 (7%)	
Unknown	0	1 (3%)	3 (2%)	
Venous invasion from primary	**29**	**31**	**125**	
Absent	24 (83%)	26 (84%)	108 (87%)	0.751[‡]
Present	5 (17%)	5 (16%)	14 (11%)	
Unknown	0	0	3 (2%)	
Surgery type to primary	**29**	**31**	**125**	
Partial glossectomy	1 (3%)	3 (10%)	29 (23%)	**<0.001**[‡]
Hemiglossectomy	0	3 (10%)	18 (14%)	
Lateral pharyngeal resection	9 (31%)	15 (48%)	33 (27%)	
Soft palate (<50%)	0	1 (3%)	12 (10%)	
Soft palate (>50%)	0	1 (3%)	3 (2%)	
Posterior pharyngeal wall	0	0	3 (2%)	
Other	19 (66%)	8 (26%)	27 (22%)	
Reconstruction to primary	**29**	**31**	**125**	
Primary closure	4 (14%)	4 (13%)	21 (17%)	NC
Skin graft	0	1 (3%)	3 (2%)	
Deltoid pectoralis flap	0	0	4 (3%)	
Pectoralis major flap	1 (3%)	1 (3%)	14 (11%)	

Radial forearm flap	6 (21%)	15 (49%)	27 (22%)	
Tongue flap	0	0	4 (3%)	
Buccal flap	0	0	4 (3%)	
Jejunal flap	1 (3%)	5 (16%)	9 (7%)	
Submandibular skin flap	1 (3%)	0	1 (1%)	
Lateral arm flap	0	0	1 (1%)	
Other	0	0	1 (1%)	
Unknown	16 (56%)	5 (16%)	36 (29%)	

IQR; interquartile range, NC; not calculable, HPVN; human papillomavirus negative, HPVP; human papillomavirus positive, HPVU; human papillomavirus unknown.

†Includes 9 patients with unknown p16 status following testing.

‡Fisher's Exact Test, bold values indicate statistical significance, 2-sided $p<0.05$, replaces Pearson Chi-square as default test when ≥20% of cells have an expected count less than five.

§Kruskal-Wallis test used to compare the median for multiple groups.

¶Includes 5 patients in the P16 not tested group and 1 patient in the P16 negative group treated with radiotherapy plus adjuvant surgery.

‖In the P16 not tested group, there are 3 patients treated with brachytherapy only, with 7 combined with conventional radiotherapy.

Table 3: Treatment outcomes

	HPVP (n=140)	**HPVN (n=51)**	**HPVU† (n=409)**	**p-value**
Treatment response				
Complete response	136 (97%)	43 (84%)	349 (85%)	**0.009**‡
Partial response	1 (1%)	4 (8%)	28 (7%)	
Stable disease	0	0	8 (2%)	
Progressive disease	3 (2%)	4 (8%)	21 (5%)	
Unknown	0	0	3 (1%)	
Local recurrence				
No	127 (91%)	39 (76%)	293 (72%)	**<0.001**‡
Yes	11 (8%)	7 (14%)	62 (15%)	
Persistent disease	2 (1%)	5 (10%)	51 (12%)	
Unknown	0	0	3 (1%)	
Time to local failure§, months, median (IQR)	7.3 (5.3-19.8)	6.7 (3.3-9.0)	6.7 (0-13.6)	0.401‖
Site for local recurrence§	**13**	**12**	**113**	
Surgical area	1 (8%)	4 (33%)	12 (11%)	**0.049**‡
Radiation area	6 (46%)	6 (50%)	77 (68%)	
Surgical and radiation area	5 (38%)	2 (17%)	13 (11%)	
Initial observation area	1 (8%)	0	11 (10%)	
Nodal recurrence				
No	123 (88%)	40 (78%)	328 (80%)	0.276‡
Yes	12 (9%)	5 (10%)	42 (10%)	
Persistent disease	5 (3%)	6 (12%)	36 (9%)	
Unknown	0	0	3 (1%)	
Time to nodal failure§, months, median (IQR)	14.0 (4.4-23.3)	3.9 (0-15.2)	4.9 (0-10.0)	**0.021**‖
Site for nodal recurrence§	**17**	**11**	**78**	
Ipsilateral node	15 (88%)	7 (64%)	49 (63%)	0.299‡

Contralateral node	2 (12%)	3 (27%)	13 (17%)	
Bilateral node	0	1 (9%)	15 (19%)	
Unknown	0	0	1 (1%)	
Metastasis				
No	125 (89%)	43 (84%)	367 (90%)	0.501
Yes	15 (11%)	8 (16%)	42 (10%)	
Time to metastasis, months, median (IQR)	14.7 (12.0-23.7)	10.2 (3.5-21.1)	8.7 (5.0-19.4)	0.199‖
Site of metastasis¶	**15**	**8**	**42**	
Lung	8 (53%)	5 (63%)	23 (55%)	1.000‡
Liver	3 (20%)	1 (13%)	12 (29%)	0.757‡
Bone	5 (33%)	4 (50%)	14 (33%)	0.653
Other	5 (33%)	3 (38%)	11 (26%)	0.777‡
New primary				
No	134 (96%)	40 (78%)	287 (70%)	**<0.001**
Yes	6 (4%)	11 (22%)	122 (30%)	
Time to new primary, years, median (IQR)	1.9 (0.6-3.3)	2.5 (1.2-8.6)	3.9 (1.6-8.6)	0.150‖
Site of new primary¶	**6**	**11**	**122**	
Head and neck	1 (17%)	3 (27%)	64 (53%)	0.191‡
Lung	1 (17%)	5 (46%)	28 (23%)	0.327‡
Other	5 (83%)	4 (36%)	42 (34%)	0.056‡

IQR; interquartile range, NA; not applicable, HPVN; human papillomavirus negative, HPVP; human papillomavirus positive, HPVU; human papillomavirus unknown.

†Includes 9 patients with unknown p16 status following testing.

‡Fisher's Exact Test, bold values indicate statistical significance, 2-sided p<0.05, replaces Pearson Chi-square as default test when ≥20% of cells have an expected count less than five.

§Includes patients with recurrence and persistent disease.

¶Not mutually exclusive, patients may have multiple sites of metastases or new primaries.

‖Kruskal-Wallis test used to compare the median for multiple groups.

Table 4: Treatment for recurrence and follow up.

	HPVP (n=140)	**HPVN (n=51)**	**HPVU† (n=409)**	**p-value**
Recurrent treatment	**22**	**20**	**138**	
No treatment	4 (18%)	4 (20%)	46 (33%)	0.475‡
Surgery	6 (28%)	7 (35%)	33 (24%)	
Radiotherapy	4 (18%)	3 (15%)	20 (15%)	
Surgery plus adjuvant radiotherapy§	4 (18%)	2 (10%)	8 (6%)	
Chemotherapy	4 (18%)	4 (20%)	31 (22%)	
Response to recurrent treatment	**18**	**16**	**92**	
Complete response	8 (44%)	10 (62%)	37 (40%)	0.376‡
Partial response	2 (11%)	0	3 (3%)	
Stable disease	1 (6%)	0	4 (5%)	
Progressive disease	7 (39%)	6 (38%)	48 (52%)	
Second local recurrence	**18**	**16**	**92**	
No	9 (50%)	13 (81%)	36 (39%)	**0.041‡**
Yes	2 (11%)	1 (6%)	14 (15%)	
Persistent disease	7 (39%)	2 (13%)	42 (46%)	
Time to second local recurrence, months,	14.3 (7.5-	6.7 (3.9-6.7)	11.3 (6.8-22.2)	0.486‖

median (IQR)	36.2)			
Ultimate local failure				
Ultimate local control	128 (91%)	46 (90%)	308 (75%)	**<0.001**‡
Ultimate local fail	12 (9%)	5 (10%)	98 (24%)	
Unknown	0	0	3 (1%)	
Time to ultimate local failure, months, median (IQR)	15.6 (8.1-36.3)	4.6 (2.2-11.1)	9.5 (6.3-19.1)	**0.043**ǁ
Second nodal recurrence	**18**	**16**	**92**	
No	11 (61%)	10 (62%)	53 (58%)	1.000‡
Yes	2 (11%)	2 (13%)	11 (12%)	
Persistent disease	5 (28%)	4 (25%)	26 (28%)	
Unknown	0	0	2 (2%)	
Time to second nodal recurrence, months, median (IQR)	29.1 (9.8-42.8)	7.0 (3.9-16.3)	9.0 (5.7-18.8)	0.125ǁ
Ultimate nodal failure				
Ultimate nodal control	131 (94%)	42 (82%)	342 (84%)	**0.028**‡
Ultimate nodal fail	9 (6%)	9 (18%)	62 (15%)	
Unknown	0	0	5 (1%)	
Time to ultimate nodal failure, months, median (IQR)	29.1 (12.5-41.0)	4.6 (3.3-11.6)	7.2 (5.2-12.3)	**0.004**ǁ
Follow up status				
Alive	98 (70%)	8 (16%)	54 (13%)	**<0.001**‡
Dead, due to head and neck cancer	26 (18%)	17 (33%)	149 (36%)	
Dead, not due to head and neck cancer	15 (11%)	26 (51%)	204 (50%)	
Dead, cause unknown	1 (1%)	0	2 (1%)	
Follow up interval, years, median (IQR)	2.6 (1.6-6.0)	2.2 (0.9-4.6)	4.2 (1.4-9.3)	**0.008**ǁ
Survival interval, years, median (IQR)¶	2.5 (1.6-5.1)	1.1 (0.5-3.1)	7.7 (6.1-12.9)	**<0.001**ǁ
Death interval, years, median (IQR)¶	3.4 (1.5-6.2)	2.4 (0.9-8.2)	3.4 (1.1-8.8)	0.338[e]

IQR; interquartile range, NA; not applicable, HPVN; human papillomavirus negative, HPVP; human papillomavirus positive, HPVU; human papillomavirus unknown.

†Includes 9 patients with unknown p16 status following testing.

‡Fisher's Exact Test, bold values indicate statistical significance, 2-sided $p<0.05$, replaces Pearson Chi-square as default test when ≥20% of cells have an expected count less than five.

§Includes 1 patient treated with radiotherapy plus adjuvant surgery.

¶Survival interval for 160 alive patients, and death interval for 440 deceased patients.

ǁKruskal-Wallis test used to compare the median for multiple groups.

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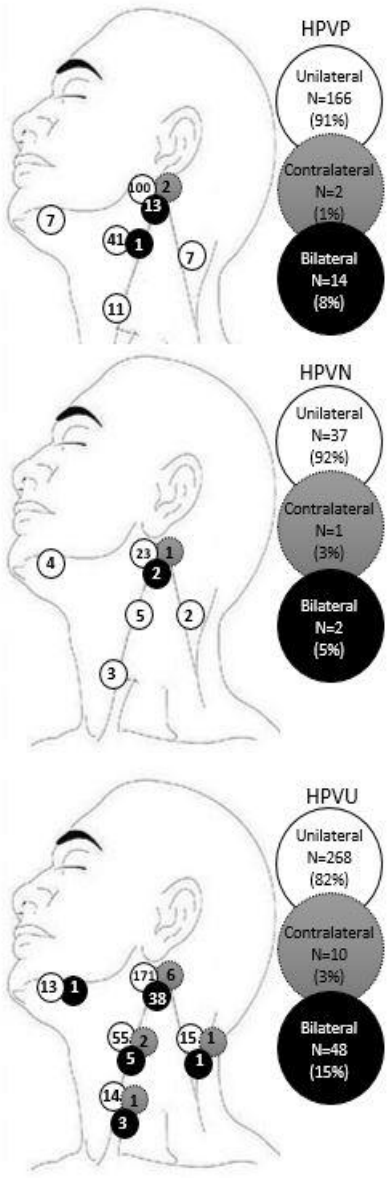

Figure 1: Site of nodal involvement by HPV status.

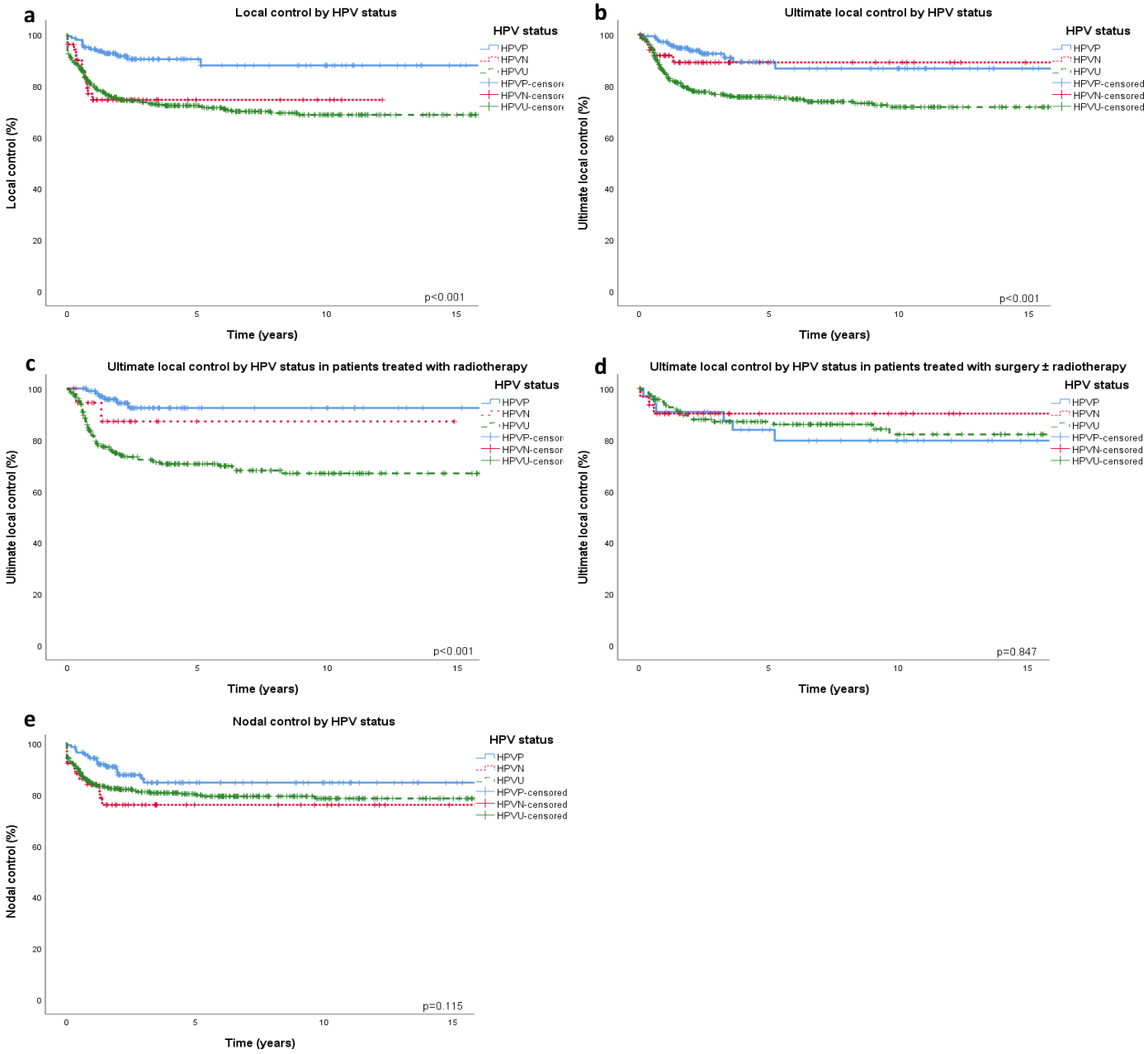

Figure 2: Tumour control by HPV status a) local control (whole cohort), b) ultimate local control (whole cohort), c) ultimate local control in patients treated with radiotherapy, d) ultimate local control in patients treated with surgery, and e) nodal control (whole cohort).

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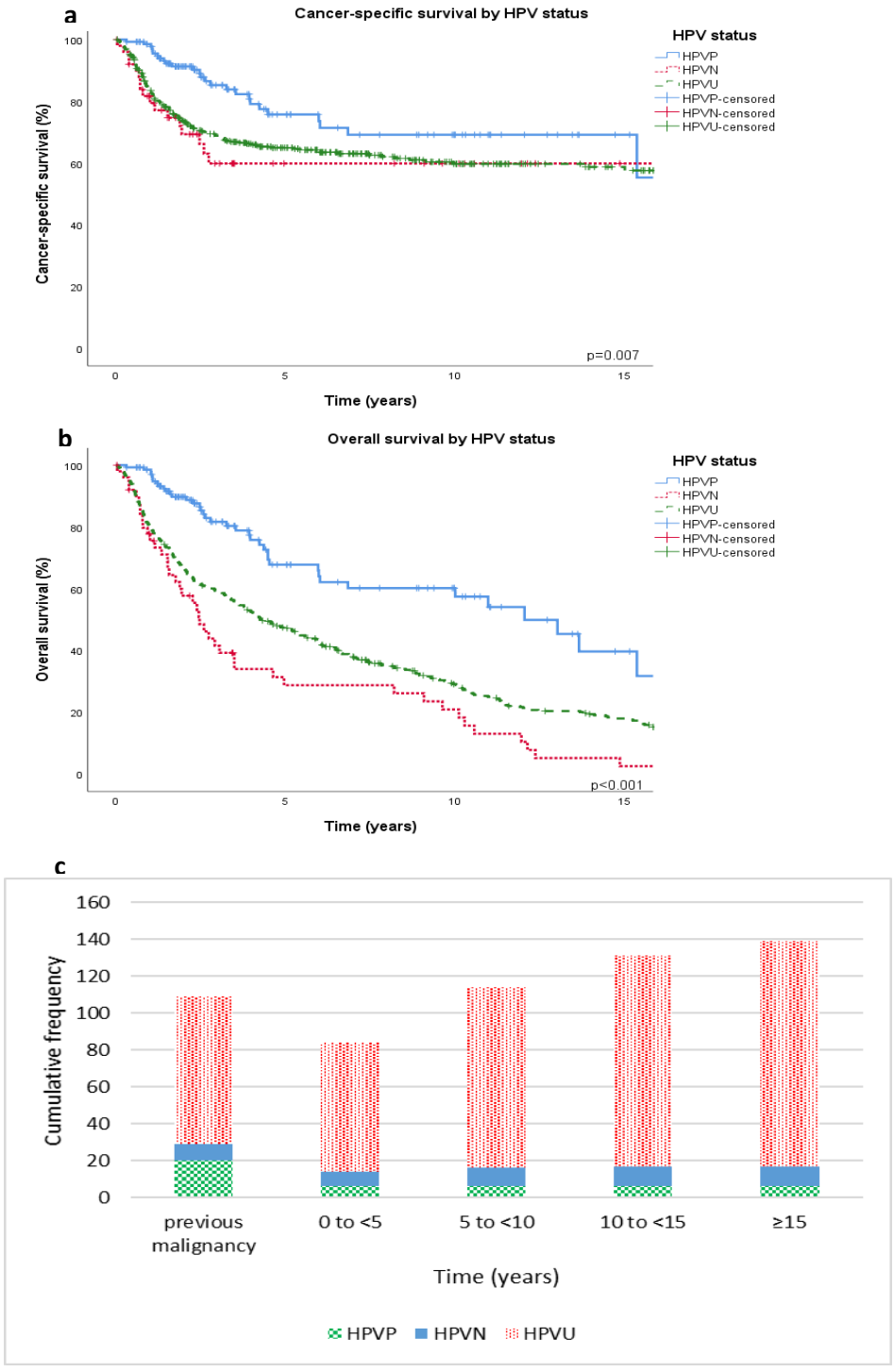

Figure 3: Survival by HPV status, a) cancer-specific survival, b) overall survival, and c) time to new primary by HPV status.

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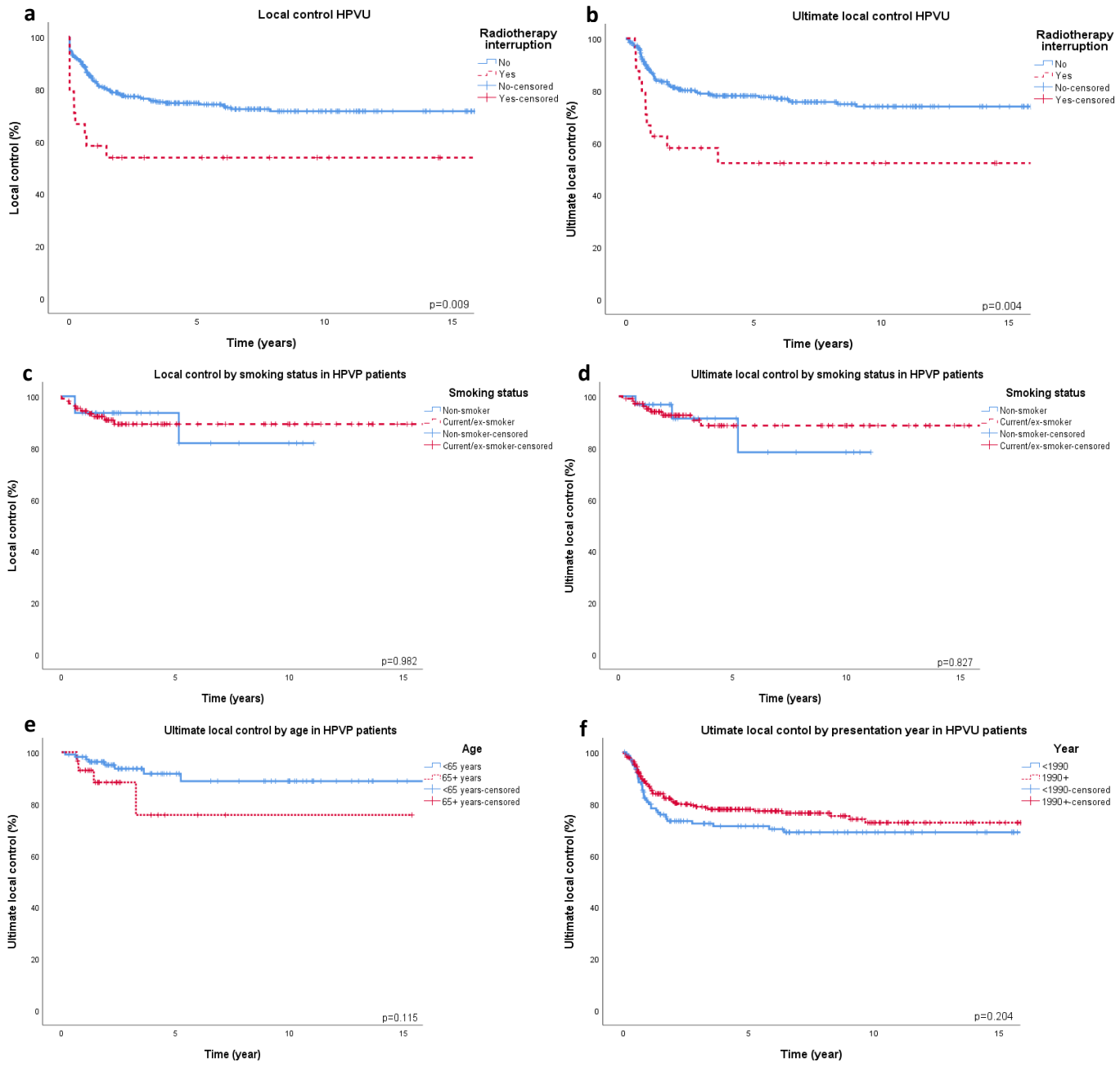

Figure 4: Tumour control by radiotherapy interruption in the HPVU group a) local control, and b) ultimate local control, by HPV status, c) local control by smoking status in HPVP patients, d) ultimate local control by smoking status in HPVP patients, e) ultimate local control by age in HPVP patients, and f) ultimate local control by presentation in HPVU patients

DISCUSSION

There are two notable features when assessing epidemiological features relating to Oropharyngeal Squamous Cell Carcinomas (OPSCC). Firstly, the incidence is increasing, [34] and secondly, the outcomes are improving. [12,35] Both factors relate to the recognition that the majority of OPSCC are now HPV-related malignancies. This feature is not applicable to p16 positive non-oropharyngeal patients. [12] There is a parallel between the prevalence of HPV carriers worldwide and the increased incidence of HPV-related OPSCC. [36] There is a link to changing sexual practices in westernised countries over the last 30-40 years. [5] The older patterns of smoking and alcohol related cancers still exists, now constituting the minority of OPSCC, however, these agents are still the dominant causative agent for non-OPSCC sites. [2,37]

Once this aetiological agent was recognised, retrospective evaluations of study populations demonstrated the importance of this subgroup in determining outcomes. Analysis of RTOG0129 (a randomised phase III study evaluating the impact of different radiotherapy fractionation patterns) demonstrated a statistically significant improvement in OS, irrespective of the fractionation approach. [24,26] This feature is reflected in the outcomes of many other studies, to the extent that de-escalation of treatment is being evaluated in clinical trials, [38] as well as a new staging classification. [39] This feature is applicable to both surgical and non-surgical approaches. [17]

The results in this audit demonstrate better outcomes relating to the primary and secondary endpoints. The contributing factors are best addressed by considering the patient, disease, and treatment categories. The patient: patients with HPVP disease are more likely to be male, non or ex-smokers, have lower alcohol consumption, and have a normal performance score. [40] The disease: HPVP patients are more likely to have resectable, poorly differentiated, and T1-T2 disease, be node positive, and N2 extent of nodal disease, [9] and (as specified by UICC 7th edition) more likely to be stage III disease. HPVN tumours were more likely to have perineural infiltration. [41] The treatment: chemoradiotherapy was more likely to be used as definitive treatment, a higher radiotherapy dose delivered (reflecting more likely the nodal extent) with more fractions over a shorter time period. It is noteworthy that HPV positivity in the oropharynx relates to a tonsillar or base of tongue origin, not as applicable to other oropharyngeal subsites, for example, soft palate origin. [5,42]

In recent years, the modes of treatment have changed, with surgery transitioning to a trans-oral robotic surgery-based approach, and radiotherapy to a more conformal approach based around CT imaging and IMRT approaches. However, using 1990 as a division point, there was no difference in outcomes by any measure pre and post this time point.

There is strong literature evidence supporting younger, fitter, and non-smoking patients as having better outcomes within all groups and sites of origin of head and neck SCC (HNSCC). [7] However, the HPVP patients have more significant nodal disease, traditionally a factor conveying a worse outcome. [12] There are biological explanations for the higher likelihood of nodal disease without portending a worse outcome, reflected in the UICC 8th edition staging reclassification. [39] This biological difference is reflected in this study whereby the time (median) to local and nodal failure is shorter in the HPVN patients. There is also evidence pointing to a

more radiosensitive cancer cell in HPVP cancers. [10] Even HPVP patients who do not complete their radiotherapy course have more favourable outcomes. [43] The fact that more patients who were HPVP had chemoradiotherapy in this review does not indicate a superior outcome for this approach. Within the literature, comparable outcomes are reported amongst all subgroups with other factors such as cost-effectiveness, being a determinant in some decision making approach's. [22]

In this treated population, 27% of HPVN patients had worse outcomes, representing a different patient population, for example, a greater proportion of current or recent smokers. The impact of smoking is very real, as evidenced by the fact that the HPVP patient who is a recent or current smoker has an outcome likelihood different to the HPVP patient, with CSS halfway between the HPVP and the HPVN population. [13-15] Despite this feature not being demonstrated in this series, it may merely represent smaller patient numbers, although reported in other studies. [44] The confounding factor may be age, with evidence suggesting older HPVP patients may not do as well as younger HPVP patients, [16,45] although not evident in this audit.

The limiting feature in this audit is the timeframe over which these patients were treated. There has been a great expansion of imaging and treatment approaches. However, over more than 30 years at this centre, patient data has been collected for the POWHN database, allowing extensive evaluation of many patient, disease, and treatment factors. All patients are clinically staged irrespective of the availability of pathological details.

CONCLUSION

OPSCC is not one disease, there are many variables that define the disease and outcomes to treatment. As with so many other HNSCCs, cigarette smoking is central to this diversity. Not only is it more likely to result in the cancer being HPVN, but also led the HPVP smoking patients to have worse outcomes, despite the same treatment. The non-smoking HPVP patient, as detailed here, despite presenting with more significant nodal disease (traditionally an adverse factor), has outcomes that result in more cures than other HNSCCs. There is commonality across smaller and larger centres that treat these patients. This behoves a reclassification of the disease (as has happened), and a greater focus on survivorship, since these patients are likely to survive for many years following treatment.

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