



Utility of a repeat PET/CT scan in HPV-associated Oropharyngeal Cancer following incomplete nodal response from (chemo)radiotherapy

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ABSTRACT

Objectives: To assess the utility of a repeat positron emission tomography/computed tomography (PET/CT) instead of immediate neck dissection (ND) for incomplete nodal response (IR) in Human Papillomavirus (HPV)-associated oropharyngeal squamous cell carcinoma (OPC) following chemoradiotherapy/radiotherapy [(chemo)RT].

Materials and methods: Patients with non-distant metastatic, node positive (N+) disease treated between Jan/2005 to Jan/2016, achieved complete response at the primary with no distant relapse on a 12-week re-staging PET/CT were evaluated. Patients underwent surveillance after complete nodal response (CR). Patients with IR underwent repeat PET/CT at 16 weeks to direct neck management. Primary endpoints were CR conversion rate and subsequent regional failure following a 16-week PET/CT directed ND. Secondary endpoints were predictive values (PV) of the 12- and 16-week PET/CT for residual nodal disease, predictors for requiring the 16-week PET/CT, 5 year regional, locoregional failure free survival (FFS) and overall survival (OS).

Results: 235 patients were evaluated. Median follow up was 56 (range 19–60) months. 41 patients underwent 16-week re-staging PET/CT, 29 (71%) converted to CR. No subsequent regional failures occurred following a 16-week PET/CT directed ND. Positive and negative PV of the 12- and 16-week PET/CT for residual nodal disease was 12% & 98%, and 33% & 97%, respectively. N-category (AJCC/UICC 7th edition) predicted for requiring a 16-week PET/CT on univariate analysis (P-value 0.02). 5 year regional, locoregional FFS and OS was 95.8%, 93.4% and 90.8%, respectively.

Conclusion: For N+ HPV-associated OPC achieving IR on the 12-week re-staging PET/CT following (chemo)RT, a repeat 16-week PET/CT can spare patients from unnecessary surgery.

Introduction

The management of the neck following radiotherapy (RT) with or without chemotherapy [(chemo)RT] for node positive (N+) mucosal head and neck cancer varies amongst institutions [1]. Institutions that direct management of the neck based on treatment response assessment with a re-staging 18F-Fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) scan have largely based this approach on the predictive values (PV) of this scan, in particular the high negative PV [2–4]. This approach has gained support from

randomized controlled trial data, which showed non-inferior outcomes compared to planned neck dissection [5].

Previously reported positive and negative PV of re-staging PET/CT scans for treatment response assessment have largely been based on a heterogeneous population of Human Papillomavirus (HPV)-associated oropharyngeal squamous cell carcinoma (OPC), non HPV-associated OPC and non-OPC sites [6–8].

Since HPV-associated OPC have more favourable outcomes following (chemo)RT than non-HPV disease and have low rates of nodal failure [9,10], the pre-test probability of residual nodal disease

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following the 12-week re-staging PET/CT differs between the two disease entities.

With a current focus on treatment de-intensification in HPV-associated OPC, it remains necessary to characterize the optimal response assessment strategy and PV of the re-staging PET/CT scan specifically for this cohort of patients, to spare the morbidity of undergoing an unnecessary post chemo(RT) neck dissection (PTND) [11,12].

We thus sought to assess the utility of a repeat 16-week re-staging PET/CT to direct management of the neck in HPV-associated N+ OPC patients with positive or equivocal residual nodal avidity (incomplete nodal response) at the 12-week re-staging PET/CT following (chemo) RT, rather than proceeding to an immediate PTND.

Materials and methods

Study population

This was a retrospective analysis of a prospectively collected database of histopathologically confirmed, locoregionally confined HPV-associated OPC patients treated with a pre-defined stage-based chemo (RT) protocol at our institution between January 2005 and January 2016. This time period coincided with the routine use of PET directed management of the neck following (chemo)RT for head and neck cancer at our institution and a minimum follow up period of 18 months from the close-out date. Patients had a minimum evaluation with a staging FDG PET/CT, panendoscopy, biopsy of the primary or involved node, and discussion at our Multidisciplinary Tumor Board with management determined by consensus.

HPV association was determined on the basis of p16 immunohistochemistry (IHC) of the biopsy specimen. IHC was performed using paraffin-embedded tumor tissue and defined as positive if there was strong and diffuse nuclear and cytoplasmic staining in > 70% of tumor. From 2010, all OPC patients underwent p16 IHC status at the time of diagnosis, while patients treated prior to this time period underwent retrospective analysis of p16 status. Patients with occult (T0) primary lesion despite biopsies of the oropharynx but had p16 positive core biopsy of an involved node were registered in this database.

Patients were included in this study if they had N+ disease, achieved a complete response at the primary site with no evidence of distant relapse on the re-staging 12-week PET/CT following (chemo)RT and underwent surveillance of the neck. This inclusion criterion was chosen on the basis that it is this group that most benefits from the appropriate selection for a PTND. This study received institutional ethics approval.

Treatment protocol

All patients were planned to receive definitive RT, typically 70 Gy to gross disease and 56 Gy to elective nodal sites over 7 weeks. Concurrent systemic therapy prescribed was Cisplatin (100 mg/m²) in weeks 1, 4 and 7 of RT. Patients unsuitable for Cisplatin were offered Cetuximab (loading dose 400 mg/m² and 250 mg/m² weekly with RT) or did not undergo systemic therapy, but were prescribed RT to 68 Gy to gross disease and 54.4 Gy to elective nodal sites over 6 weeks. From December 2013, eligible patients were enrolled onto the Trans-Tasman Radiation Oncology Group (TROG) low-risk HPV-associated OPC de-escalation trial (TROG 12.01, NCT01855451) and randomized to receive either concurrent weekly Cisplatin (40 mg/m²) or Cetuximab (as described above) with RT to 70 Gy to gross disease and 54 Gy to elective nodal sites over 7 weeks.

The contralateral neck was electively treated for patients with pre-defined high risk features including T3-T4 tumors, tumors that crossed midline, base of tongue tumors (any T-stage), bulky ipsilateral N2b disease (presence of > 4 cm node/s or more than 3 nodes involved) or N3 disease, based on the 7th edition American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) TNM

staging.

Patients were treated with either Intensity Modulated RT (IMRT) or Volumetric Modulated Arc Therapy (VMAT). All RT plans underwent quality assurance assessment by the head and neck radiation oncology team to ensure compliance with treatment protocol and appropriate tumor coverage.

FDG PET/CT response assessment and management

Following completion of treatment, patients underwent a 12-week re-staging FDG PET/CT scan for response assessment. Scans were interpreted locally by consensus of a PET/CT specialty radiologist and nuclear medicine physician through visual inspection. Focal FDG uptake that had greater intensity than background liver activity on PET imaging and corresponded to a structural abnormality in the neck on co-registered CT imaging were reported as positive for residual nodal disease. Focal FDG uptake below background liver activity but had greater intensity than adjacent normal tissue activity on PET imaging and corresponded to a structural abnormality in the neck on co-registered CT imaging were reported as equivocal for residual nodal disease. No residual FDG avidity above adjacent normal tissue activity or diffuse FDG uptake on PET imaging without corresponding suspicious structural abnormality on co-registered CT imaging was reported as complete nodal response (CR). Standardized Uptake Values (SUV) were not routinely recorded for each restaging FDG PET/CT scan as these were not used for assessment of treatment response and has not been shown to improve diagnostic accuracy compared with visual inspection [13,14]. For this study, all re-staging FDG PET/CT interpreted by consensus of a PET/CT specialty radiologist and nuclear medicine physician and reported as positive or equivocal for residual nodal disease were classified as an incomplete nodal response (IR).

Patients who had a CR following the 12-week re-staging PET/CT underwent clinical surveillance, and patients who had an IR were re-evaluated at our Multidisciplinary Tumor Board with subsequent management determined by consensus. For HPV-associated OPC, our general policy for IR following the 12-week re-staging PET/CT is to repeat a PET/CT scan at 16-weeks provided there is a complete response in the primary site, no evidence of distant disease and no clinical progression of nodal disease. Following the 16-week re-staging PET/CT, patients who had a persistent IR were re-evaluated at our Multidisciplinary Tumour Board and typically recommended PTND by consensus.

Follow-up schedule

Patients were clinically assessed every 3 months post treatment for the first year, every 4 months for the subsequent 2 years and every 6 months for 2 more years. Following the restaging PET/CT scan/s, re-imaging was performed if there was suspicion of recurrence on clinical examination.

Statistical considerations

The closeout date for this study was 1st August 2017. Patient outcomes were evaluated up to a maximum of 5 years through reviewing medical records and obtaining outcomes from treating physicians. The primary end points were to determine the conversion rate to CR following a 16-week re-staging PET/CT and subsequent regional failure rate following PTND as indicated by IR on the repeat 16-week scan. Secondary endpoints were to determine the PV of the 12- and 16-week re-staging PET/CT for residual nodal disease using 2x2 tables, measured against histopathology of the PTND if performed or a minimum clinical follow-up of 18 months, clinical predictors of requiring a 16-week PET/CT, the 5 year regional, locoregional failure free survival (FFS) and overall survival (OS). Univariate analysis to identify clinical predictors of requiring a 16-week PET/CT was performed using Chi-Square tests

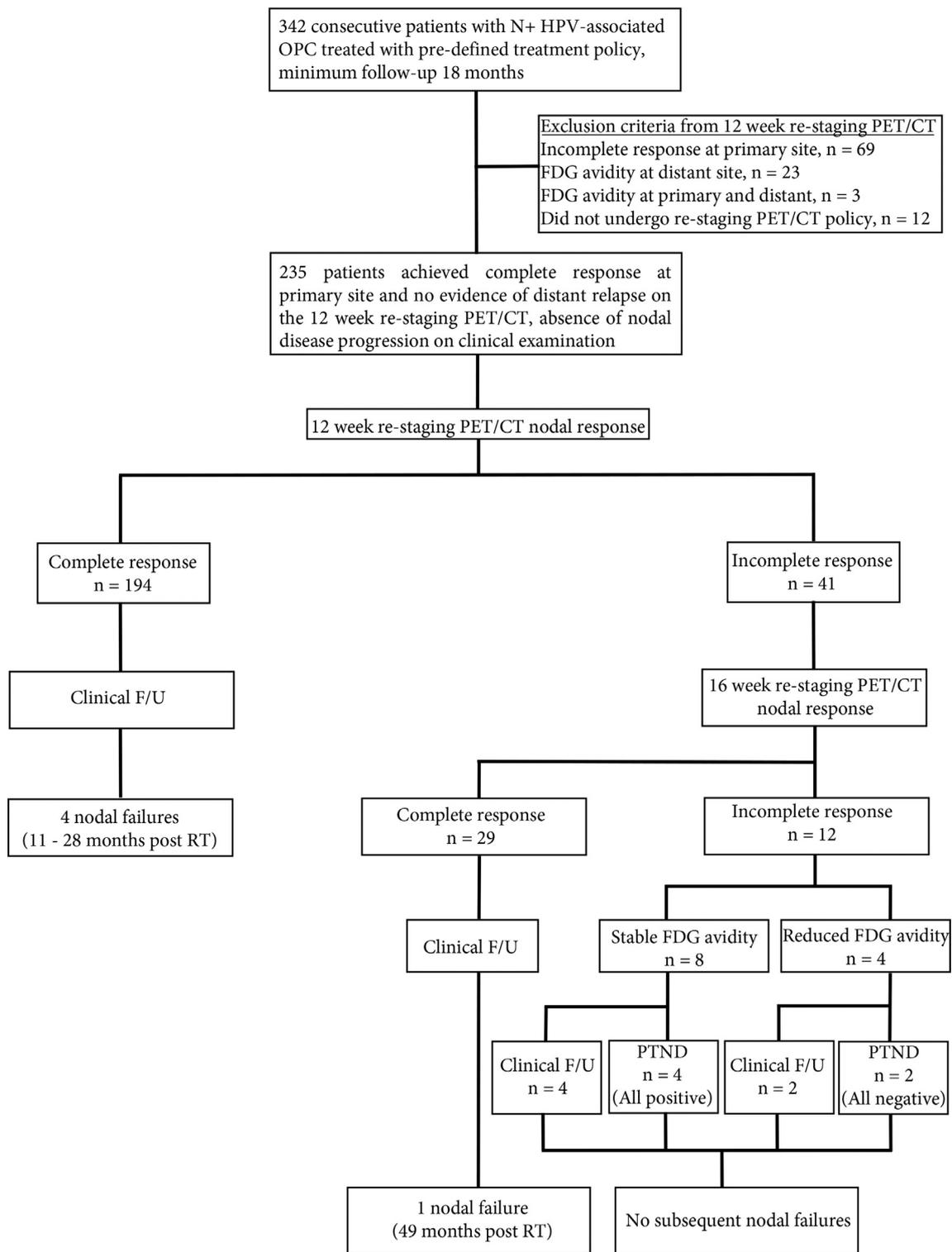


Fig. 1. Study population and treatment outcomes. N+: Node positive, HPV: Human Papillomavirus, OPC: Oropharyngeal squamous cell carcinoma, PET/CT: Positron emission tomography/computed tomography, FDG: Fluorodeoxyglucose, F/U: Follow-up, RT: Radiotherapy, PTND: Post treatment neck dissection.

(or Fisher’s exact test when appropriate). The Kaplan-Meier method was used to estimate the FFS and OS from the date of commencement of RT until failure, death or date of last follow-up. Statistical analyses were performed using the R statistical software and p-values with $p < 0.05$ were considered statistically significant [15].

Results

Patient, Tumor & treatment characteristics

342 consecutive patients with HPV-associated OPC underwent our pre-defined treatment protocol, a 12-week re-staging FDG PET/CT for response assessment and had a minimum of 18 months follow-up. 235 (69%) patients were identified as meeting the inclusion criteria during

Table 1
Baseline patient characteristics.

Characteristic	N = 235
Age – median years (range)	58 (21–89)
Gender	Female 22 (9.4%) Male 213 (90.6%)
T-category AJCC/UICC 7th ed. – no. (%)	T0 – 10 (4.3%) T1 – 52 (22%) T2 – 89 (37.9%) T3 – 46 (19.6%) T4a – 34 (14.5%) T4b – 4 (1.7%)
N-category AJCC/UICC 7th ed. – no. (%)	N1 – 31 (13.2%) N2a – 29 (12.3%) N2b – 108 (46%) N2c – 49 (20.9%) N3 – 18 (7.6%)
Stage AJCC/UICC 7th ed. – no. (%)	III – 27 (11.5%) IVa – 187 (79.6%) IVb – 21 (8.9%)
N-category AJCC/UICC 8th ed. – no. (%)	N1 – 168 (71.5%) N2 – 49 (20.8%) N3 – 18 (7.7%)
Stage AJCC/UICC 8th ed. – no. (%)	I – 124 (52.8%) II – 61 (25.9%) III – 50 (21.3%)
Radiotherapy dose – Gy (%)	66 – 8 (3.4%) 68 – 22 (9.4%) 70 – 205 (87.2%)
Systemic therapy – no. (%)	Yes – 221 (94%) Cisplatin – 176 (75%) Cetuximab – 45 (19%) No – 14 (6%)

AJCC/UICC: American Joint Committee on Cancer / Union for International Cancer Control.

the defined time period. (Fig. 1) Baseline characteristics are described in Table 1. The median age was 58 years (21–89). The majority were male (90.6%), the predominant AJCC/UICC 7th edition T- and N-category and stage was T2 (37.9%), N2b (46%) and stage IVa (79.6%), respectively. The predominant AJCC/UICC 8th edition N-category and stage was N1 (71.5%) and stage I (52.8%), respectively. Systemic therapy was delivered in 94% of patients. The median follow-up was 56 (19–60) months.

12-week PET/CT nodal response

194 (83%) patients had a CR at the 12-week re-staging PET/CT and underwent clinical surveillance. Four of these patients had subsequent nodal failure at 11, 13, 18 and 28 months post treatment (Fig. 1).

16-week PET/CT CR conversion rate and nodal failure rate following PTND

41 (17%) patients had an IR at the 12-week re-staging PET/CT and underwent repeat re-staging PET/CT scan at 16 weeks post (chemo)RT (Fig. 1).

29 (71%) of these patients converted to a CR on the 16-week re-staging PET/CT scan and underwent clinical surveillance. One patient who had N3 disease, a smoking history of > 10 pack years and was clinically surveilled following CR at the 16-week re-staging PET/CT, developed nodal failure at 49 months post treatment and was successfully salvaged with neck dissection and post-operative re-irradiation.

12 (29%) patients had persistent IR at the 16-week re-staging PET/CT. Of these patients, six underwent PTND after consensus recommendation from our Multidisciplinary Tumor Board. Four patients had residual nodal disease on histopathology and had unchanged FDG avidity in the involved node at the 16-week compared to the 12-week re-staging PET/CT. Two patients with negative PTND had shown reduction in FDG avidity of the suspected residual node at the 16-week

Table 2
Sensitivity, Specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of the 12-week re-staging PET/CT scan for residual nodal disease.

Nodal status	Disease recurrence	Disease controlled	
12 week PET CR	4	190	NPV: 98%
12 week PET IR	5	36	PPV: 12%
	Sensitivity: 56%	Specificity: 84%	

CR: complete nodal response, IR: incomplete nodal response.

compared to the 12-week re-staging PET/CT scan. There were no subsequent nodal failures following PTND.

Of the six patients who did not undergo PTND for persistent IR following the 16-week scan, four patients had stable FDG avidity in the residual nodal structure compared to the 12-week re-staging PET/CT scan and were recommended PTND from our Multidisciplinary Tumor Board but refused a PTND. The remaining two patients had reduced FDG avidity in the residual nodal structure at the 16-week compared to the 12-week re-staging PET/CT scan, had sub-centimeter residual nodal structure, and was recommended clinical observation by consensus from our Multidisciplinary Tumor Board. There were no subsequent nodal failures in these six patients that did not undergo PTND.

Sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of re-staging PET/CT

For the 12-week restaging PET/CT scan, the sensitivity, specificity, PPV and NPV for residual nodal disease was 56%, 84%, 12% and 98%, respectively. For the 16-week re-staging PET/CT scan, the sensitivity, specificity, PPV and NPV for residual nodal disease was 80%, 78%, 33% and 97%, respectively (Tables 2 and 3).

Clinical predictors of requiring a 16-week PET/CT

Of the clinical factors assessed in univariate analysis as predictors for requiring a 16-week PET/CT, only N-category (N3 vs N1-2) based on the AJCC/UICC 7th edition TNM staging was a significant predictor for a repeat re-staging scan (p-value 0.02) (Table 4).

Neck dissection rate and tumor outcomes

Our response assessment policy utilizing a 12-week re-staging PET-CT scan, repeat 16-week re-staging PET-CT scan for IR and re-evaluation at our Multidisciplinary Tumor Board resulted in an overall PTND rate of 2.6% (6 patients). Performing an immediate PTND for IR on the 12-week re-staging PET-CT scan would increase the PTND rate to 17% (41 patients).

At the close out date, there were nine (3.8%) nodal failures, of which five (2.1%) were isolated and four (1.7%) were non-isolated nodal failures (with either primary or distant relapse).

The 5 year regional FFS, locoregional FFS and OS in this cohort was 95.7% (95% CI 93–98.6%), 93.3% (95% CI 89.6–97.1%) and 90.7% (95% CI 86.6–95%), respectively (Fig. 2A–C).

Table 3
Sensitivity, Specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of the 16-week re-staging PET/CT scan for residual nodal disease.

Nodal status	Disease recurrence	Disease controlled	
16 week PET CR	1	28	NPV: 97%
16 week PET IR	4	8	PPV: 33%
	Sensitivity: 80%	Specificity: 78%	

CR: complete nodal response, IR: incomplete nodal response.

Table 4

Univariate analysis of clinical factors as predictors for requiring a repeat re-staging 16-week PET/CT for incomplete nodal response on the restaging 12-week PET/CT.

Univariate analysis	No. of patients restaged with 12-week PET alone	No. of patients restaged with 12- & 16-week PET	P-value
<i>N-category</i>			
N3	11	7	0.02*
N1-2	183	34	
<i>Concurrent systemic therapy</i>			
Yes	184	37	0.28
No	10	4	
<i>Type of systemic therapy</i>			
Cisplatin	145	31	0.66
Cetuximab	39	6	
<i>T-category</i>			
T4	40	8	1
T1-3	154	33	
<i>Smoking history</i>			
Never	62	8	0.17
< 10 pack years	40	13	
≥ 10 pack years	92	20	
<i>Gender</i>			
Female	20	2	0.38
Male	174	39	

T- and N-category were recorded according to the American Joint Committee on Cancer/Union for International Cancer Control 7th edition TNM staging.

* Statistically significant.

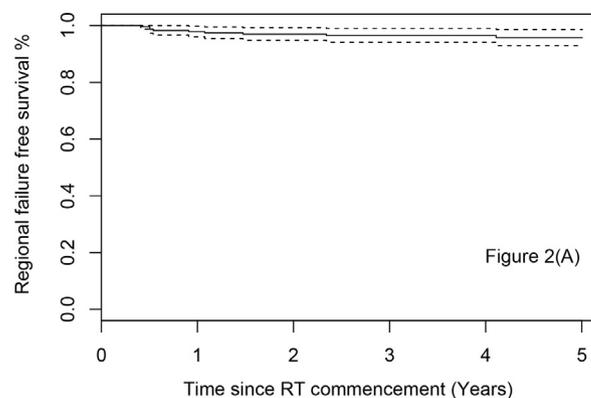
Discussion

The primary objective of this study was to assess the utility of a repeat 16-week re-staging PET/CT scan to direct management of the neck following IR on a 12-week re-staging scan in a cohort of N+ HPV-associated OPC treated uniformly with a pre-defined (chemo)RT protocol. We found that deferring the decision to undergo PTND until persistent IR is shown on a repeat 16-week re-staging PET/CT can reduce the rate of unnecessary PTND and had no detrimental impact on subsequent regional control.

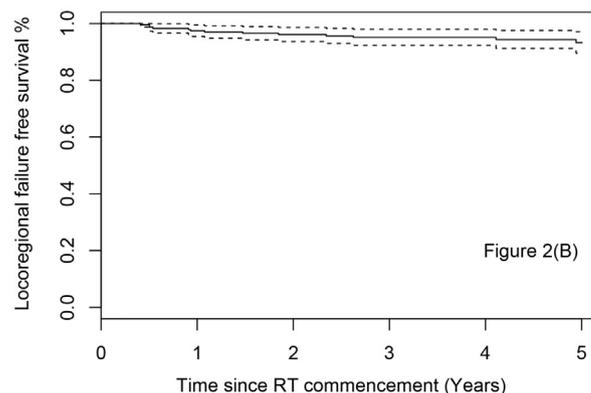
The utility of the re-staging FDG PET/CT scan for response assessment following (chemo)RT in N+ head and neck squamous cell carcinoma (SCC) has consistently been shown to spare PTND without compromising outcomes due to the high NPV of this scan [2,3,5]. The re-staging PET/CT to direct management of the neck following (chemo)RT has routinely been performed at a minimum 12 weeks post therapy due to lower NPV for re-staging scans performed earlier [16]. This practice is accepted internationally in expert consensus guidelines [17,18]. For neck nodal response assessment, our results were consistent with previously reported high NPV of the re-staging PET/CT at 12 weeks in HPV-associated OPC treated with (chemo)RT, and our results showed that NPV remained high with a re-staging PET/CT at 16 weeks [19].

In our cohort, the 5 year regional FFS was high at 95.8%, similar to previously reported rates of 94% in a large single institutional series [10]. Our PTND rate however, was considerably lower at 2.6% than previously reported (20%) when following our institutional re-staging PET/CT response assessment policy to direct management of the neck [10]. Given the focus on de-intensification therapy in HPV-associated OPC, improving identification of patients who require PTND is one method of limiting treatment morbidity.

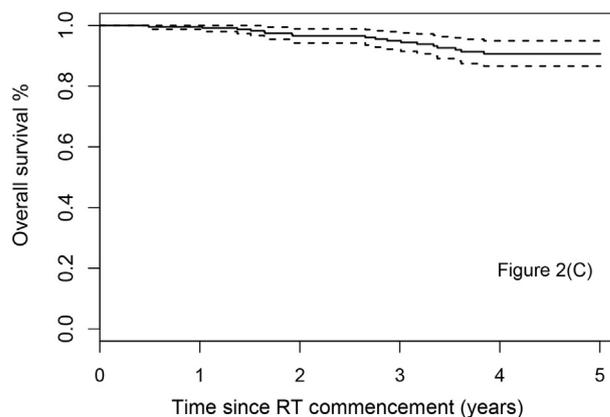
It is important to note that this study was not testing the efficacy of (chemo)RT in HPV-associated OPC. However, since HPV-associated OPC have consistently shown favourable prognosis following (chemo)RT, the pre-test probability of residual nodal disease following the 12-week re-staging PET/CT scan is likely lower than non HPV-associated OPC or non OPC sites [9,10,20–22]. This would contribute to the low PPV of 12% for residual nodal disease found in our cohort with the 12-week re-staging PET/CT, which is similar to previously reported PPV in



Number at risk
235 229 205 172 127 85



Number at risk
235 228 204 171 126 84



Number at risk
235 234 210 177 129 85

Fig. 2. (A–C). Kaplan-Meier estimates of (A) Regional failure free survival following radiotherapy (RT) with or without systemic therapy [(chemo)RT], (B) Locoregional failure free survival following (chemo)RT, (C) Overall survival following (chemo)RT.

a cohort of HPV-associated OPC [19]. This is in contrast to the significantly higher PPV of 52% reported in meta-analyses of a heterogeneous group of mucosal head and neck carcinoma [7]. The PPV of the repeat 16-week re-staging PET/CT scan remains low at 33%, albeit improved from the 12-week re-staging scan. More importantly, 71% of patients who underwent the repeat 16-week re-staging PET/CT,

converted to a CR and avoided an unnecessary neck dissection. Furthermore, there was no subsequent regional failures for patients who had a deferred decision to undergo a PTND until a 16-week re-staging PET/CT was performed, indicating that these patients had a successful PTND at this deferred time point. This is consistent with the findings of Goguen et al. [23], where neck dissections performed less than 12 weeks compared to 12 weeks or more after (chemo)RT had no difference in regional relapse or complication rates.

In the PET-NECK study, patients in the 12-week re-staging PET/CT surveillance cohort underwent PTND for IR, which included equivocal PET/CT findings, following (chemo)RT for N+ head and neck SCC [5]. PET/CT surveillance had non-inferior overall survival compared to planned neck dissection in the PET-NECK study, but surveillance was more cost-effective and Mehanna et al. [5] commented that the advantage of surveillance may have been underestimated in HPV-associated disease given the decision to undergo PTND following the 12-week re-staging scan. Our results supports this and suggests that for N+ HPV-associated OPC following (chemo)RT, the decision to proceed with PTND for IR can be deferred until a repeat 16-week re-staging PET/CT is performed, provided there is no clinical evidence of nodal disease progression. By repeating the PET/CT at 16 weeks, this can improve differentiating residual nodal disease from post therapy changes and minimize unnecessary surgical intervention in patients that show an IR on the 12-week re-staging PET/CT [11,24].

Although the diagnostic accuracy of delaying initial response assessment with PET/CT to 16 weeks post (chemo)RT in head and neck SCC has been reported with high NPV (99%), our results show a comparable high NPV of 98% for residual nodal disease following a 12-week restaging PET/CT in HPV-associated OPC [11]. Given the high NPV and to limit patient anxiety whilst awaiting response assessment, we recommend patients with N+ HPV-associated OPC treated with (chemo)RT, to undergo a 12-week re-staging PET/CT for initial treatment response assessment [25]. For patients with complete response in the primary, no distant disease and an IR on the 12-week PET/CT but no clinical evidence of disease progression, a repeat 16-week re-staging PET/CT should then be performed to guide management of the neck.

In our study, the low PPV of the re-staging PET/CT scans and N-category (AJCC/UICC 7th edition) as the only clinical factor predicting for a repeat PET/CT at 16 weeks suggests a prolonged resolution of FDG avidity in the involved node(s) in HPV-associated OPC following treatment. This has similarities to what has been reported for CT response assessment, with slower involution of nodal disease seen in HPV-associated OPC [26]. In our cohort, patients with IR at the 16-week restaging PET/CT had no subsequent nodal failure if there was a reduction in FDG avidity in the suspected node at 16 weeks compared to the 12-week scan. For the eight patients who had unchanged FDG avidity in the involved node between the two re-staging scans, four underwent PTND and all had residual nodal disease, whilst the other four patients who were recommended PTND but refused, underwent clinical observation and had no subsequent nodal failure. Due to the few patients that had persistent and unchanged FDG avidity between the 12- and 16-week re-staging PET/CT, it is unclear whether a surveillance strategy is feasible for these patients. Our recommendation is for these patients to undergo a PTND following the 16-week re-staging PET/CT.

Although the PTND rate was low in this cohort, a limiting step to improving the diagnostic accuracy of re-staging PET/CT scans to direct management of the neck is the absence of a validated standardized reporting criteria or PET derived quantitative parameter criteria specifically for HPV-associated OPC [16]. The Hopkins criteria has been validated as a reliable standardized reporting criteria for PET/CT treatment response assessment following (chemo)RT in the ECLYPS study, however a heterogeneous group of HPV-associated OPC, non HPV-associated OPC and non-OPC sites were included [27]. This should be a focus of investigation, given the availability of software packages that can provide SUV quantification across imaging platforms, and the

interest in de-intensification therapy, requiring improvements in patient selection for PTND to avoid the unnecessary additional treatment morbidity [28].

Conclusion

In summary, our study suggests for patients with N+ HPV-associated OPC treated with (chemo)RT that have an IR at the 12-week re-staging PET/CT scan, deferring the decision for PTND until a repeat 16-week restaging PET/CT scan can spare patients from unnecessary surgery with no detrimental impact to subsequent regional control.

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Conflict of interest

None declared for all authors.

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