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12 week PET-CT has low positive predictive value for nodal residual disease in human papillomavirus-positive oropharyngeal cancers

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ABSTRACT

Objectives: Surveillance PET-CT scans at 12 weeks post-radiotherapy for head and neck cancer can be used to omit neck dissections with no detriment in overall survival. Human Papillomavirus (HPV) driven tumours behave differently on conventional imaging after radiotherapy but it is unknown if this effect is seen on PET-CT and if HPV status affects the accuracy of PET-CT. We aimed to determine the negative and positive predictive values (NPV and PPV) of 12 week surveillance PET-CT in HPV positive and negative tumours, and investigate predictors of relapse in equivocal responders.

Materials and methods: A retrospective cohort study in a UK tertiary level oncology hospital, between 2013 and 2016 included adults with oropharyngeal squamous cell carcinoma, or HPV positive head and neck squamous cell cancers of unknown primary, treated with radiotherapy.

Results: The PPVs of 12 week PET-CT in HPV positive and negative disease are 30% and 81.8% respectively ($p < 0.01$). The NPVs of 12 week PET-CT in HPV positive and negative disease are 92.9% and 55.6% respectively ($p < 0.01$). 67% of HPV positive patients with equivocal responses on 12 week PET-CT achieved complete response by 24 weeks. Equivocal responses in HPV positive disease had statistically similar survival to patients with complete responses. Comparing disease and imaging characteristics, there were no predictors of residual tumour.

Conclusions: HPV positive tumours have a poor PPV of 30% on 12 week surveillance PET-CTs and take longer to achieve complete response. A period of further surveillance can be considered instead of an immediate neck dissection in this group of patients.

Introduction

There are over 12,000 new diagnoses of head and neck cancer in the UK annually, with 62% found at a late stage [1]. For stage III or IV (UICC/AJCC TNM staging system 7th edition) tumours of the oropharynx, treatment traditionally involved radiotherapy (with or without chemotherapy) and a neck dissection. The practice changing PET-Neck study demonstrated that neck dissections could be omitted in patients who had a complete response on ^{18}Fluorodeoxyglucose positron emission tomography-computed tomography (PET-CT) at 12 weeks after completion of radiotherapy with no detriment on survival [2]. This study divided patients into complete, equivocal and incomplete responders on the basis of a 12 week PET-CT response. Patients with equivocal or incomplete responses were mandated to have neck dissections, whilst those with a complete response underwent clinical surveillance. This is now routine clinical practice [3].

The PET-Neck study did not stratify the patients by Human Papillomavirus (HPV) status, but commented that it may be possible to delay neck dissections in patients with HPV positive disease with equivocal responses, for two reasons. Firstly, tumour HPV status is a significant prognostic factor, with HPV positive tumours having a 3-year survival of 82% compared to 57% in HPV negative tumours [4].

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Secondly, HPV positive tumours respond differently on computed tomography (CT) or magnetic resonance imaging (MRI) compared to HPV negative tumours, shrinking to a greater degree by 12 weeks, but then taking longer to completely involute compared to HPV negative disease, in some cases up to 36 weeks [5].

A recent meta-analysis demonstrated that PET-CTs have an excellent negative predictive value (NPV) of 95–97%, but a relatively poor positive predictive value (PPV) of 64–69% [6]. This study also found that the diagnostic accuracy of the PET-CT was better when the imaging was performed after 3 months, compared to less than 3 months, but was not able to analyse this by HPV status. Therefore, whilst HPV positive tumours have a better prognosis and take longer to respond on anatomical imaging, there is a lack of information on the accuracy of 12 week PET-CTs depending on HPV status. As PET-CT surveillance is now standard practice, this information is important as it affects the decision whether to proceed to a neck dissection (with attendant risks and side-effects) or continue with surveillance.

The aim of this retrospective study is to identify the PPV for residual disease of 12 week surveillance PET-CT in HPV positive and negative oropharyngeal squamous cell cancers, and investigate the equivocal responders group to identify if there are any predictors of residual disease.

Methods

Ethical considerations

This study used anonymised patient information, gathered retrospectively and therefore was exempt from the regional ethical committee review.

Patients

This is a retrospective review from the Beatson West of Scotland Cancer Centre, a tertiary level oncology hospital which has a catchment area of 2.4 million patients. Patients with biopsy-proven oropharyngeal squamous cell cancer (OPSCC) or HPV positive cancer of unknown primary (HPV + CUP), were treated using radical radiotherapy (with or without chemotherapy) and underwent surveillance PET-CT scanning were identified from the PET radiology database. Patients were excluded if they had node-negative disease, or unknown HPV status. Treatment and patient characteristics were identified from electronic clinical records. Patients were staged using the UICC/AJCC TNM staging system 7th edition. HPV status was determined using HPV DNA in 87.4% of patients and positive p16 staining in 12.6% (where staining of greater than 70% was considered positive).

Treatment

All patients received radical radiotherapy, with a dose of 65 Gray in 30 fractions to areas with known disease, and 54 Gy in 30 fractions to prophylactic nodal levels, selected as per international guidelines [7,8]. All patients were planned using the Eclipse™ treatment planning system (Varian Medical System, Palo Alto, US) and were treated with volumetric arc therapy (VMAT). Patients who received platinum-based induction chemotherapy and/or platinum-based or cetuximab concurrent chemotherapy were included.

Follow-up

Patients were clinically reviewed at 6 weeks, 12 weeks then every 2–3 months post-radiotherapy where they would undergo clinical examination and flexible naso-endoscopy if indicated. All patients underwent surveillance ^{18}Fluorodeoxyglucose (FDG) PET-CT scans, scheduled to take place 12 weeks after the end of radiotherapy. Other imaging modalities (CT, MRI, ultrasound) were used at the clinician's discretion during the period of follow-up. The 12 week surveillance PET-CT scans were interpreted qualitiatively by nuclear medicine radiologists who graded the scans as showing either an incomplete (maximum standardised uptake value (SUV_{max}) greater than the reference hepatic uptake value regardless of nodal size), equivocal (SUV_{max} greater than blood pool but less than hepatic uptake in a normal size node or no FDG uptake in an enlarged node) or complete response (no enlarged nodes or FDG uptake) according to the PET-Neck protocol. For the purposes of PPV and NPV testing, equivocal and incomplete responses were positive tests and complete responses were negative tests. Equivocal or incomplete responders were discussed in multi-disciplinary team meetings (MDTs). Individualised treatment decisions were made regarding neck dissections, further investigations (e.g. ultrasound guided biopsy) or ongoing surveillance.

In order to look for possible predictors of residual disease in patients with equivocal responses, the SUV_{max} was collected by the nuclear medicine radiologists. The nodal gross tumour volume (GTVn) was calculated from the radiotherapy planning CT scan before treatment. The percentage reduction of lymph nodes was derived by identifying the longest diameter of the largest lymph node on the radiotherapy planning CT, and comparing it to the longest diameter of the same lymph node on the 12 week PET-CT.

Relapse was defined as either pathologically proven residual or recurrent disease in neck nodes or distant metastases, or neck or distant metastases identified on serial imaging.

Statistical analysis

The PPV, NPV, sensitivity and specificity of the 12 week PET-CT were calculated with 95% confidence intervals and compared using a two-sample proportion test. Relapses in the HPV positive incomplete and equivocal responders were compared with a Fisher's exact test. Predictive factors for relapse were compared using t-tests for continuous variables and Chi-squared tests for categorical variables. Survival between the difference response groups were calculated using the Kaplan-Meier method and compared using a log-rank test. Overall survival time was taken from the time of first radiotherapy treatment. All tests used a two-tailed significance level of 5%. Statistical calculations were performed using SPSS version 23 (IBM, Armonk, US).

Results

Baseline characteristics

From January 2013 to September 2016, 155 patients were identified with node positive OPSCC/HPV + CUP treated radiotherapy with or without chemotherapy. All patients completed radiotherapy. Baseline characteristics are shown in Table 1. 87% had HPV positive disease and 86% had N2 or N3 disease. For the whole group, median age was 57 (range 39–82) and median follow-up was 32.3 months (range 0.4–57.7). There were no non-smokers in the HPV negative group, which is consistent with the natural history of the disease.

12 week PET-CT responses and PPV/NPV

All patients had an end of treatment surveillance PET-CT at a median time of 90 days post treatment (range 43–284 days). 34 patients developed recurrent disease over the course of follow-up (21 HPV positive patients (15.6%) and 13 HPV negative patients (65%)), see Table 2. The PPVs of 12 week PET-CT in HPV positive and negative disease are 30% (95% CI 22.6–38.7%) and 81.8% (95% CI 56.9–93.9%) respectively ($p < 0.01$, two sample proportional test). The NPVs of 12 week PET-CT in HPV positive and negative disease are 92.9% (95% CI 86.9–96.3%) and 55.6% (95% CI 32.8–76.2%) respectively ($p < 0.01$, two sample proportional test). The specificity and sensitivity of 12 week PET-CT for both HPV positive and negative disease is

Table 1
Baseline characteristics demonstrating the only significant differences between the HPV positive and negative group was regarding smoking history. *Smoking history only available for 153 patients. †There were two administrative errors where patients had CT scans at 3 months instead of PET-CT, hence the PET-CT scans at 284 and 187 days. Another administrative error resulted in a patient having a PET-CT at 43 days post-radiotherapy, and a patient had a PET-CT at 55 days due to clinical concerns regarding resectability of disease.

		Total n = 155, (%)	HPV positive n = 135, (%)	HPV negative n = 20, (%)	
Gender	*Male*	74.2	100 (74.1)	15 (75)	p = 0.93 (Chi-sq test)
	Female	25.8	35 (25.9)	5 (5)	
Mean age (years, range)			57.8 (39–82)	61.4 (45–78)	p = 0.12 (*t*-test)
T-classification	*T0-T2*	97 (62.6)	85 (62.9)	12 (60)	p = 0.80 (Chi-sq test)
	T3-T4	58 (37.4)	50 (37.1)	8 (40)	
N-classification	*N1*	22 (14.2)	17 (12.6)	5 (25)	p = 0.25 (Chi-sq test)
	N2	128 (82.6)	113 (83.7)	15 (75)	
	N3	5 (3.2)	5 (3.7)	0 (0)	
Smoking*	*Never*	61 (39.9)	61 (45.9)	0 (0)	p < 0.01 (Chi-sq test)
	Current/Former	92 (60.1)	72 (54.1)	20 (1 0 0)	
Mean time to PET-CT (days, range)			102 (43–284†)	97.7 (55-187†)	p = 0.66 (*t*-test)
Mean follow-up (months, range)			33.1 (0.4–57.5)	26.1 (6.9–50.3)	p = 0.06 (*t*-test)

Table 2
Relapses by HPV status. CR (Complete response), EQR (Equivocal response), ICR (Incomplete response).

HPV positive	No relapse (%)	Relapse (%)	
CR	79	6	85
EQR/ICR	35	15	50
	114 (84.4)	21 (15.6)	135
HPV negative			
CR	5	4	9
EQR/ICR	2	9	11
	7 (35)	13 (65)	20

69.3% and 71.3%.

To explore why the PPV was low in HPV positive disease, the group was divided into equivocal and incomplete responders (Table 3). The PPV was 20% and 50% for HPV positive and negative disease respectively. There was a significant difference in the rate of relapse between equivocal and incomplete responders (p = 0.049, Fisher's exact test).

Outcome of HPV positive patients with equivocal responses

Fig. 1 shows the ongoing management of the 34 HPV positive patients with equivocal responses on 12 week PET-CT. Two-thirds of patients had delayed imaging by 6 months that showed either a complete response or no suspicious signs of active malignancy. The 6 month imaging modality were as follows: repeat PET-CT (13), ultrasound (6), CT (3) and MRI (1). There were no relapses in this group. However, nine patients (26%) had repeat imaging at six months which was suggestive of residual disease. Three patients had a pathologically negative neck dissection, three patients had a pathologically positive neck dissection, two patients refused neck dissection and one patient had a neck dissection and developed metastatic disease at two years after completion of radiotherapy. Two further patients did not have imaging at 6 months: one patient had a pathologically positive neck dissection at 4 months and one patient underwent clinical surveillance after MDT discussion. Both patients are alive and relapse free. In total, 27 (79.4%) HPV equivocal responders proved to be disease free in the neck at 6 months.

Table 3
HPV positive equivocal responders divided by relapse status.

HPV positive		No relapse	Relapse	
Response	*Equivocal*	27	7	p = 0.049
	Incomplete	8	8	
		35	15	

Predictors of relapse in the HPV positive equivocal responders

On univariate analysis, there were no significant baseline factors that were associated with relapse. There was no significant difference in percentage nodal reduction, volume of initial GTVn and SUV_{max} between the relapse and non-relapse group (see Table 4).

Overall survival

Median overall survival was not reached in the HPV positive complete, equivocal and incomplete responders. There was no difference in survival between the complete and equivocal responders but the incomplete responders had a significantly shorter survival compared to the equivocal responders (log-rank test p = 0.011, shown in Fig. 2).

Discussion

Synopsis of key/new findings

These data demonstrate that 12 week surveillance PET-CTs have a poor PPV of 30% in HPV positive patients, which is significantly different to HPV negative tumours. This is partially due to 67% of HPV positive equivocal responders having a delayed complete response on imaging at 6 months, and 79.4% of this group being disease free in the neck on follow-up. The overall survival of HPV positive equivocal responders is not significantly different to complete responders. There were no disease characteristics that were associated with relapse in the HPV positive group.

Comparisons with other studies

This study cohort shows that 12 week surveillance PET-CTs have a high NPV, which is in concordance with the PET-Neck study, and previous meta-analyses [6,9]. Our data also support the observation that HPV positive disease takes longer than 3 months to reach a complete radiological response, not only on conventional imaging but also on PET-CT. A recent study has compared the PPV of surveillance PET-CTs performed at 12 weeks and at 16 weeks in HPV positive oropharyngeal cancers, showing that the PPV rises from 12% to 33%, and that 71% of patients with equivocal or incomplete responses converted to a complete response over the 4 week period, similar to the 67% at 6 months post-treatment in our study [10]. Repeating the PET-CT at 16 weeks maybe considered too early, given that in our data, complete response was seen by 6 months, and in studies using non-metabolic imaging, complete response in HPV positive patients were seen at 36 weeks. The timing of ongoing surveillance beyond the 12 week PET-

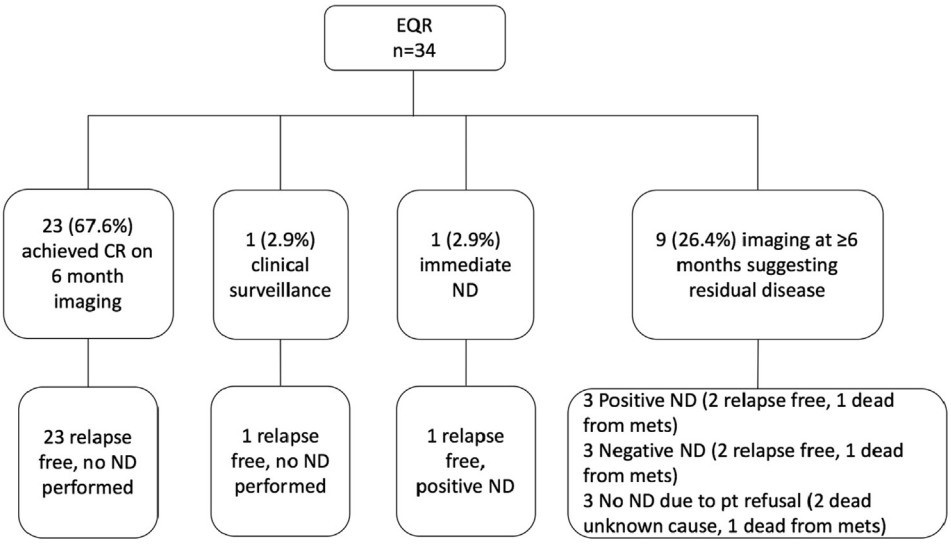

Fig. 1. Flow diagram of HPV positive patients who had an equivocal response on 12 week PET-CT.

CT is controversial in HPV positive disease. Later scanning may benefit patients by reducing the number of unnecessary neck dissections, however, this must be balanced by maintaining the option of early detection and salvage neck surgery. Moreover, it may contribute to psychological distress experienced by patients as they await investigations to assess outcome from treatment.

The survival of the HPV positive complete or equivocal responder group is over 90% at 3 years, which is consistent with many studies, and has led to calls for treatment de-escalation in this group [11]. Our data has shown that, even in HPV positive disease, there is a group of patients who have an incomplete response and do significantly worse, suggesting that reduction in treatment may not be beneficial for all HPV positive tumours. To try to identify patients with residual disease in the HPV positive equivocal responders, we analysed the SUV_{max}. The mean SUV_{max} in both the relapse and non-relapse group was 3.6, whereas in a previous study, a SUV_{max} of less than 2 was associated with no residual disease [12]. This highlights the issue that both residual tumour and post-radiotherapy inflammation can cause FDG uptake, making PET-CT interpretation difficult.

Strengths and limitations of the study

This study is the first study to look specifically at the HPV positive equivocal responder subgroup. It demonstrates that these patients could be managed differently to HPV positive incomplete responders as survival in this group is similar to complete responders. It supports the current practice of offering neck dissections to patients with incomplete responses regardless of HPV status. It provides evidence that HPV positive disease takes longer to respond on metabolic imaging, supporting the conclusions of Liu *et al.*, in a larger cohort of patients and collected over a shorter period of time. This implies that the HPV positive equivocal responder group represents slowly resolving disease and further surveillance may be appropriate. This study is also the first to analyse if there are any disease specific factors that could predict for relapse in patients who have an equivocal response on surveillance imaging.

There are several limitations to this study. This is a retrospective review with short follow-up and a modest sample size. Only 18 patients in the EQR group have a follow-up of 36 months or above, therefore there is a risk that the overall survival may be worse in this group over a longer period of observation. Combining data from other oncology centres would strengthen the conclusions of this study, as well as explore possible predictors of relapse. The imaging techniques used to diagnose a complete response at 6 months were a mixture of conventional and metabolic scans, thus inconsistent. However, reassuringly there has been no relapsed disease in this group of patients suggesting that whatever modality was used, the diagnosis of no residual disease was accurate. The majority of head and neck cancers would have relapsed by 3 years post-radiotherapy and our median follow-up is 32.3 months, therefore some late relapses may not be identified. The

Table 4
Univariate analysis of disease characteristics in HPV positive patients with equivocal responses who relapsed or not.

HPV positive EQR		No neck relapse	Neck relapse	
Mean age		56.8	61.6	p = 0.097 (*t*-test)
Gender	*Female*	10	4	p = 0.436 (Fisher's exact)
	Male	30	6	
T-classification	*T0-2*	20	4	p = 0.728 (Fisher's exact)
	T3-4	20	6	
N-classification	*N1*	3	1	p = 0.753 (Chi-sq)
	N2	35	9	
	N3	2	0	
Smoking	*Never*	18	3	p = 0.478 (Fisher's exact)
	Current/former	20	7	
Concurrent Chemo	*Yes*	36	8	p = 0.586 (Fisher's exact)
	No	4	2	
Mean % nodal reduction		60.6	45.6	p = 0.08 (*t*-test)
Volume of initial GTVn (cm^3)		27.6	30.1	p = 0.84 (*t*-test)
Mean SUVmax		3.66	3.61	p = 0.94 (*t*-test)

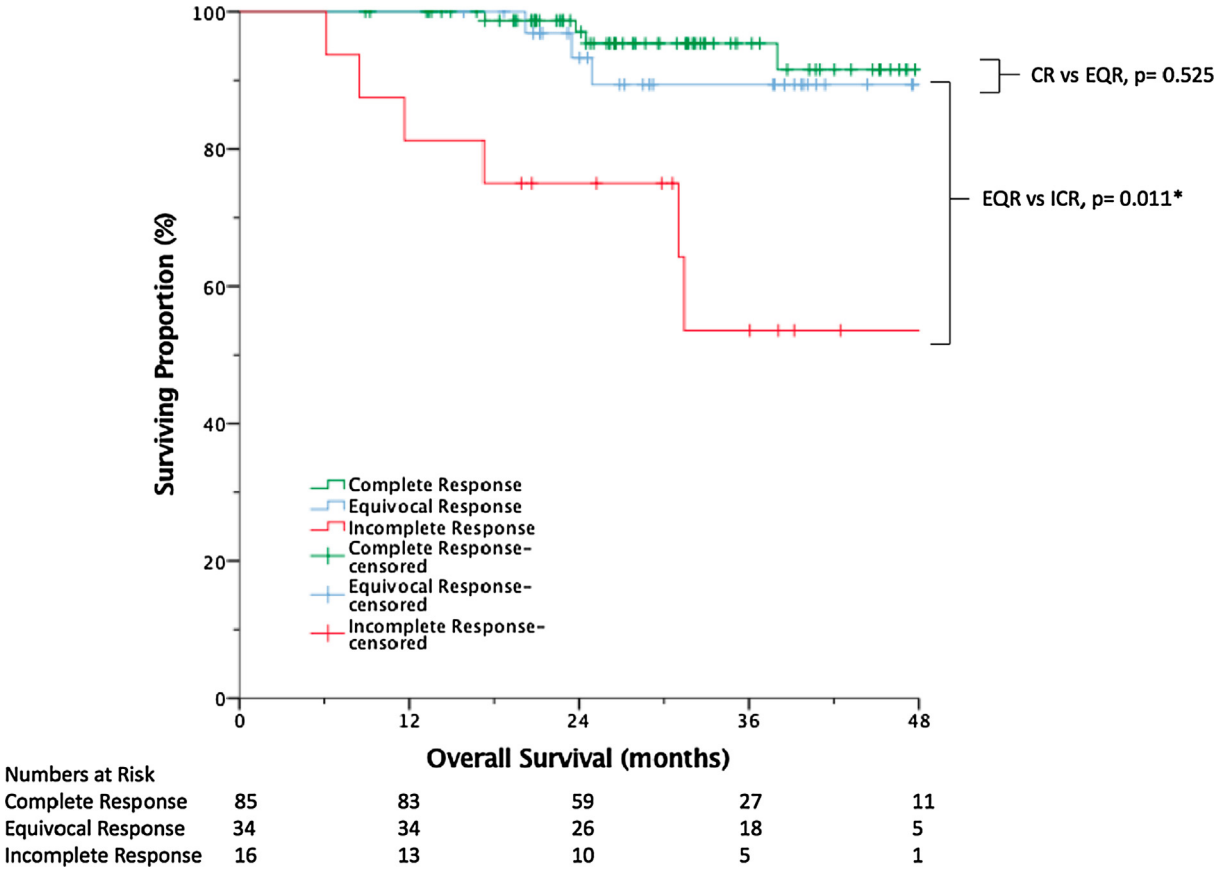

Fig. 2. A Kaplan Meier plot of the overall survival of the HPV positive patients split by 12 week PET-CT response demonstrating no significant difference between the complete and equivocal responders, but a significant difference between the equivocal responders and incomplete responders. Median overall survival was not reached in all groups.

gold standard when testing the 12 week PET-CTs would be a planned neck dissection. However, we use a surrogate marker of relapse (either a positive neck dissection or loco-regional or distant failure on serial imaging) which may under-report the actual amount of residual disease present. This surrogate marker is a reasonable outcome measure because planned neck dissections at 12 weeks may over-report the disease burden by identifying tumour cells that are in a state of senescence post-radiotherapy and would not have caused recurrent disease.

Despite these limitations, this study adds significant evidence to support a period of prolonged surveillance following radiotherapy for HPV positive oropharyngeal SCC achieving an equivocal response on 12 week PET-CT. To generate level I evidence for the management of HPV positive equivocal responders would require a large clinical trial, which is unlikely to be feasible given that this treatment paradigm has already been adopted for this group in clinical practice.

Despite the overall prognosis of HPV positive equivocal responders being good, 26% had signs of residual disease at 6 months, and further work is required to better identify this subgroup. We found no radiological predictors of relapse but emerging techniques such as measurement of circulating blood HPV DNA may prove useful as an early marker of residual disease [13].

Clinical applicability of the study

Patients with HPV positive OPSCC and an equivocal response on a 12 week surveillance PET-CT can consider surveillance rather than a neck dissection as the majority of patients will develop a complete response at 6 months. Conversely, HPV positive patients with incomplete responses and HPV negative patients with equivocal or incomplete responses should be considered for neck dissection. Further work is required to identify predictive markers of patients with HPV positive disease and equivocal responses to better target who would benefit from neck dissections.

Conclusions

In HPV positive patients, 12 week surveillance PET-CTs have a poor PPV and take longer to have a complete radiological response. Surveillance can be considered in this group of patients instead of an immediate neck dissection.

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Declaration of Competing Interest

None to declare.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2019.08.011.

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