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Second-look PET-CT following an initial incomplete PET-CT response to (chemo)radiotherapy for head and neck squamous cell carcinoma

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Abstract

Objectives

The limited positive predictive value of an incomplete response on PET-CT following (chemo)radiotherapy for head and neck squamous cell carcinoma (HNSCC) means that the optimal management strategy remains uncertain. The aim of the study is to assess the utility of a 'second-look' interval PET-CT.

Methods

Patients with HNSCC who were treated with (chemo)radiotherapy between 2008-17 and underwent i) baseline and ii) response assessment PET-CT iii) second-look PET-CT following incomplete (positive or equivocal scan) response were included. Endpoints were conversion rate to complete response (CR) and test characteristics of the second-look PET-CT.

Results

562 patients with HNSCC underwent response assessment PET-CT at a median of 17 weeks post-radiotherapy. Following an incomplete response on PET-CT, 40 patients underwent a second-look PET-CT at a median of 13 weeks (range 6-25) from first response PET-CT. 34/40 (85%) patients had oropharyngeal carcinoma. 24/40 (60%) of second-look PET-CT scans converted to a complete locoregional response. The primary tumour conversion rate was 15/27 (56%) and the lymph node conversion rate was 14/19 (74%). The sensitivity, specificity, PPV and negative predictive value (NPV) of the second-look PET-CT for were 75%, 75%, 25% and 96% for the primary tumour, and 100%, 92%, 40% and 100% for lymph nodes. There were no cases of progression following conversion to CR in the primary site or lymph nodes.

Conclusions

The majority of patients who undergo a second-look PET-CT convert to a CR. The NPV of a second-look PET-CT is high, suggesting the potential to avoid surgical intervention.

Keywords: PET-CT; head and neck cancer; radiotherapy; chemotherapy; recurrence

Keypoints

PET-CT is a useful tool for response assessment following (chemo)radiotherapy for head and neck squamous cell carcinoma

An incomplete response on PET-CT has a limited positive predictive value and optimal management is uncertain.

These data show that with a ‘second-look’ interval PET-CT the majority of patients convert to a complete metabolic response. When there is doubt about clinical and radiological response a ‘second-look’ PET-CT can be used to spare patients unnecessary surgical intervention

Abbreviations

CR = complete response

EUA = examination under anaesthetic

FDG = 2-[Fluorine-18]-fluoro-2-deoxy-D-glucose

HNSCC = head and neck squamous cell carcinoma

HPV = human papilloma virus

IMRT = intensity modulated radiotherapy

NPV = negative predictive value

PET-CT = positron emission tomography -computed tomography

PF = cisplatin and 5-fluorouracil

PPV = positive predictive value

TPF = docetaxel, cisplatin and 5-fluorouracil

Introduction

Accurate response assessment following (chemo)radiotherapy for head and neck squamous cell carcinoma (HNSCC) is required to select patients for clinical follow up from those who require surgical treatment. The difficulty in determining the significance of residual masses post-treatment limits the utility of anatomical imaging with CT and/or MRI [1]. 2-[Fluorine-18]-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography -computed tomography (PET-CT) combines anatomical and functional imaging. The recent randomised PET-NECK trial in HNSCC patients with nodal disease found a strategy of FDG PET-CT guided surveillance had non-inferior survival when compared with a planned neck dissection and was more cost effective [2]. Response assessment with FDG PET-CT following chemoradiotherapy is now a standard of care, in PET-CT imaging guidelines [3] and management guidelines [4; 5].

The negative predictive values (NPV) of response assessment FDG PET-CT have been shown to be excellent, identifying patients who do not require surgical intervention [6-14]. This applies even in the context of metabolically inactive residual masses [8; 15]. However, PET-CT scans are susceptible to false positive results, with post-radiotherapy inflammation, reactive changes and physiological uptake [16]. This results in a limited positive predictive values (PPV). A PPV of 52% was reported in a meta-analysis [17], whilst individual series have shown lower PPVs [6; 7; 10; 11; 14; 18]. In the PET-NECK trial patients with a partial or equivocal response underwent a neck dissection [2]. However, the limited PPV of response assessment FDG PET-CT suggests that a policy of intervention for all patients who do not achieve a complete response on PET-CT may represent overtreatment [14].

The optimal strategy following a positive or equivocal PET-CT response scan remains uncertain. Increasing time from completion of treatment may allow post-radiotherapy inflammatory/reactive FDG-uptake to reduce. This provides the rationale to repeat the PET-CT after a further interval. One recent series [18] reported performing a second interval FDG PET-CT in 41 patients with human papilloma virus (HPV)-associated oropharyngeal carcinoma with a 71% conversion rate to complete response.

In our centre FDG PET-CT has been used to assess response since 2008 and over time have adopted an approach of performing a ‘second-look’ PET-CT in patients with uncertainty regarding response. The aim of this report is to evaluate the accuracy and utility of a second-look FDG PET-CT.

Methods

The study involved retrospective analysis performed under a waiver of informed consent and ethics approval by the Institutional Review Board. Consecutive patients who had a FDG PET-CT performed for response assessment after (chemo)radiotherapy for HNSCC between August 2008-May 2017 were identified using an institutional database. Inclusion criteria: i) squamous cell carcinoma of oropharynx, hypopharynx, larynx, oral cavity, paranasal sinuses or unknown primary site, ii) (chemo)radiotherapy with curative intent, iii) pre-treatment FDG PET-CT, iv) FDG PET-CT as first response assessment. The subgroup of patients who had undergone a second-look FDG PET-CT performed following MDT discussion due to uncertainty regarding response status were identified for analysis. There was no institutional policy on selection of patients for a second-look PET-CT and this decision was made on the discretion of the MDT and participating clinicians. Patients were excluded from the analysis if they had undergone prior therapeutic resection.

Staging

Routine staging included nasoendoscopy, examination under anaesthetic (EUA) with biopsy if indicated, MRI and/or contrast-enhanced CT of neck, CT thorax. A pre-treatment FDG PET-CT was done to optimally stage patients and provide a baseline for interpretation of subsequent response assessment for patients who had with bulky stage II or stage III/IV disease. A specialist Head & Neck Multidisciplinary meeting routinely reviewed all imaging and assigned an American Joint Committee on Cancer TNM staging 7th edition classification [19].

Radiotherapy

A 3D-CT planned technique was utilised early in this period [20]. Intensity modulated radiotherapy (IMRT) was subsequently became standard [12; 21]. Institutional protocols were followed with daily fractionation schedules of 70Gy in 35 fractions or 65Gy in 30 fractions, with prophylactic doses of 54-63 Gy in 30-35 fractions.

Chemotherapy

A proportion of patients received induction chemotherapy with either docetaxel/cisplatin/5-fluorouracil (TPF) or cisplatin/5-fluorouracil (PF) [21]. Concurrent chemotherapy was using cisplatin 100mg/m^2 on days 1 and 29 or 1, 21 and 43.

Response assessment

Response was routinely assessed approximately 4 months post-treatment, and included clinical examination, naso-endoscopy if indicated and a FDG PET-CT. PET-CT scans were reviewed in MDT meetings were a consensus decision made regarding management for patients with less than a complete response.

FDG PET-CT protocol

FDG PET-CT scans were performed before June 2010 on a 16-slice Discovery STE PET-CT scanner (GE Healthcare), between June 2010-October 2014 on a 64-slice Philips Gemini TF64 scanner (Philips Healthcare), subsequent to October 2014 on a 64-slice Discovery 710 scanner (GE Healthcare). Patients were fasted for 6 hours prior to intravenous Fluorine-18 FDG injection. Scanning was only carried out if blood glucose was < 10 mmol/L. Acquisition of PET was performed 60-minutes following tracer injection. Physiological tracer activity was minimised within the head and neck region using a silence protocol (no talking) during the uptake period following tracer injection [22; 23]. The CT component of the scan was performed using a standard protocol (without iodinated contrast) with the following settings: 140 kV; 80 mAs; a tube rotation time of 0.5s per rotation; pitch 6; section thickness 3.75 mm.

Categorisation of FDG PET-CT response assessment

PET-CT reports were used for the analysis to categorise the FDG PET-CT response. FDG PET-CT scans were reported by experienced radiologists who were dual certified in Nuclear Medicine and Radiology. FDG PET-CT images assessment was performed qualitatively by comparison of tumour or nodal tracer activity to background physiological uptake. A semi-quantitative assessment using maximum standardised uptake value (SUV_{max}) of both residual tumour and/or nodal uptake was routinely documented. As previously described [6; 12], the first post-treatment FDG PET-CT were categorised into 'positive', 'equivocal' or 'complete response' (CR) for the primary site and lymph nodal sites separately. Sites of FDG uptake were classified as positive if the uptake was focal and corresponded to an anatomical structural abnormality with greater intensity than that of background liver. A scenario of focal uptake of greater intensity than background liver which does not correspond to a structural abnormality is not easy to define with the low dose non-contrast CT but would be commented upon by the PET-CT report for MDT discussion rather than classified as a positive scan. Scans were classed as equivocal if focal FDG uptake had reduced from baseline

imaging and was lower than liver background but higher than adjacent normal tissues. Scans were classified as negative if there was no abnormal focal FDG uptake or only diffuse FDG uptake without a corresponding anatomical abnormality on the CT and was considered radiotherapy-related. This negative response classification includes cases with a residual mass with no abnormal FDG uptake, even if there was a possible increase in size of residuum. PET-CT reports routinely included details of residual tissue even if metabolically inactive. These details would be reviewed by the clinical team/MDT and management decisions made on an individual basis. The same reporting approach was used for the second-look PET-CT.

Analysis and statistics

Duration of follow up was defined as being from final day of radiotherapy treatment. The disease status was determined from any pathology and/or radiology reports and electronic notes review of outcomes. 2x2 tables constructed using clinicopathological outcomes were used to calculate sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV).

Results

562 patients were identified with HNSCC who had undergone a baseline and response assessment PET-CT following (chemo)radiotherapy. Median time from end of radiotherapy to response assessment PET-CT was 17 weeks (range 6-31 weeks). The median baseline tumour SUV_{max} and node SUV_{max} were 11.0 (range 0-53) and 8.1 (range 0-34) respectively. On the response PET-CT, 180/562 (32%) had residual avidity at primary site, median SUV_{max} 5.7 (range 1.3-14.3). 140/562 (25%) had residual activity in regional lymph nodes with a median 3.2 (range 1-12.5). Median follow-up period was 26 months (from completion of radiotherapy (range 3-148 months)). Overall 2-year local control, regional control, distant metastasis free rate, progression free survival and overall survival were 89%, 85%, 88%, 73% and 79% respectively. 40 patients underwent a second-look PET-CT. Out of 522 did not have a second-look PET-CT, 147/522 had subsequent disease progression. Progression at the primary site occurred in 60/522, at regional lymph nodes in 80/522, and distant metastases in 67/522. This included 21 patients with progression at both the primary site and regional lymph nodes and 35/67 with distant metastases also having local and/or regional progression. Of these 522 patients, the sensitivity, specificity, PPV and NPV of the response assessment PET-CT for primary disease and lymph node disease was 79.5%, 88.8%, 57.9%, 95.7% and 71.3%, 93.1%, 68.7% and 93.8% (equivocal and positive response categories combined for purposes of analysis).

Group who underwent a second-look PET-CT (n=40)

40/562 (7%) patients underwent a second-look PET-CT scan. For each of these patients, disease status following the first response assessment PET-CT was considered by the clinical team to be uncertain. Patient, disease and treatment details for the whole cohort and the subgroup who underwent a second-look PET-CT scan are shown in **Table 1.** 34/40 (85%) patients had oropharyngeal carcinoma, and 24/34 were p16 positive, 3/34 p16 negative and 7/34 unknown p16 status. In the group of 40 patients, the median values (range) of baseline tumour SUV_{max} and node SUV_{max} were 12.0 (range 0.7-53) and 9.4 (range 2.1-34) respectively. Median time from completion of radiotherapy to first response assessment PET-CT was 16.8 weeks (range 12-20). **Table 2** details the response categories (CR, equivocal or positive) on the first response assessment PET-CT with regard to primary site and nodes for these 40 patients. All patients who underwent a second-look PET-CT had a metabolically equivocal or positive response category initial PET-CT ie. a second-look PET-CT was not utilised for patients with a metabolically inactive residual mass. On the first response PET-CT, in patients with avidity at the primary site (n=27) median tumour SUV_{max} was 4.7 (range 3.7-10.7). 24/27 of these patients had oropharyngeal carcinoma. For patients with ongoing

avidity within lymph nodes (n=19), median node SUV_{max} was 2.8 (range 1.6-7.1). 15/19 of these patients had oropharyngeal carcinoma.

The second-look PET-CT was performed at a median of 13 weeks (range 6-25) after the first response assessment PET-CT. **Table 3** provides details of response categorisation for primary tumour and nodes on the second-look PET-CT (CR, equivocal, positive). Overall 24/40 (60%) of second-look PET-CT scans converted to a complete locoregional response. The primary tumour conversion rate was 15/27 (56%); all of these 15 patients had oropharyngeal carcinoma. An example is shown in **Figure 1A**. The median primary tumour SUV_{max} on the second-look PET-CT in the 12 patients not achieving a primary tumour CR was 4.6 (range 2.2-8.5). The lymph node conversion rate was 14/19 (74%); 11 of these 14 patients had oropharyngeal carcinoma. An example is given in **Figure 1B**. The median nodal SUV_{max} on the second-look PET-CT in the 5 patients not achieving a nodal CR was 2.4 (range 1.5-3.8). Overall in these 40 patients, 4 (10%) had confirmed residual primary tumour (one of these patients had a complete response at primary site on first response PET-CT and second-look PET-CT) and 2 (5%) had lymph node disease.

Flow diagrams to illustrate outcomes of second-look PET-CT for patients with avidity at primary tumour site (n=27) and lymph nodes (n=19) on first response assessment PET-CT are shown in **Figures 2A** and **2B** respectively. The 3 patients shown in **Figure 2A** who had persistent disease at the primary site had stable PET-CT findings on the second look PET-CT (one was unfit for salvage surgery, one unresectable with a T4 posterior pharyngeal wall carcinoma at baseline and one developed lung metastases on the second-look PET-CT in addition to persistent local disease). The patient in **Figure 2B** with an equivocal nodal response on the second-look PET-CT who suffered a regional recurrence on follow up had declined a neck dissection following this PET-CT. **Table 4** shows a breakdown of second-look PET-CT response categories (CR, equivocal and positive) by primary tumour and lymph node with disease outcome, providing PPV and NPV. If equivocal and positive results are combined for analysis, the sensitivity, specificity, PPV and NPV of the second-look PET-CT for were 75%, 75%, 25% and 96% for the primary tumour, and 100%, 92%, 40% and 100% for lymph nodes.

Lung metastases were confirmed in 4/40 (10%) on the second-look PET-CT. These patients had new non-avid sub-centimetre lung nodules with the differential considered to be inflammatory/infective changes or early metastases to small to characterise on free-breathing PET (n=3) or 'inflammatory-appearing' lung changes (n=1) on the initial response assessment PET-CT in conjunction with locoregional avidity with clinical uncertainty over locoregional response.

Discussion

Response assessment FDG PET-CT is well-established following chemoradiotherapy with a high NPV at primary site and lymph nodes [7-11]. It has been shown to be possible to spare patients a neck dissection without compromising outcomes in the event of a complete response on PET-CT [2]. Although much of the focus has been in neck management, a high NPV also avoids the need for EUA/biopsy of the primary site. The optimal timing of the response assessment PET-CT is uncertain and is a trade off between scan accuracy and allowing timely surgical intervention in the event of treatment failure. Imaging early post-treatment is associated with false negative results as viable cancer cells may have insufficient time to repopulate post-treatment to be detectable by PET-CT; in addition, false positive scans are more likely due to post-radiotherapy inflammation [24]. One study demonstrated that scans <7 weeks post-treatment were less accurate than those performed later [25]. In a meta-analysis, PET scans >12 weeks post-treatment had a higher sensitivity [17]. Due to the lower NPV of earlier scans, response assessment at a minimum of 12 weeks post treatment is recommended [4; 5; 18]. A baseline PET is valuable in accurately reporting the response assessment PET-CT [26]. The approach in our centre is to perform a baseline PET-CT and assess response 16 weeks post-treatment; this has been associated with a high NPV [6; 12]. However, even when imaging at later, equivocal and positive scans are common with limited PPV [6-8; 14]. For example, in our prior report we found the PPV of equivocal nodal uptake was only 20% [6]. PPV is likely to be lower for HPV-related oropharyngeal carcinoma who have a more favourable prognosis and a lower pre-treatment probability of residual disease [18].

The objective of this study was to evaluate the utility of a repeat, second-look FDG PET-CT in guiding management following an incomplete response on the initial PET-CT response scan (including positive and equivocal scans). Overall 60% of second-look PET-CT scans converted to a complete locoregional response. The primary tumour conversion rate was 56% and the lymph node conversion rate was 74%. Critically the NPV of the second-look PET-CT was very high (96% for primary site and 100% for lymph nodes). These data demonstrate that many patients will have a complete response on a second-look PET-CT, avoiding the need for surgical intervention including biopsies, EUAs and neck dissections. The only case of primary tumour failure following a complete primary tumour response on second-look PET-CT was a patient who had had the second-look PET-CT due to positive nodal uptake and had a complete response at the primary site on the initial response scan. As shown in **Figure 2** there were no recurrences at the primary tumour site or lymph nodes which converted from incomplete response to complete response on the second-look PET-CT. With

regard to lymph node uptake, FDG avidity remained stable on the second-look PET-CT in 5/19 patients. Two underwent a neck dissection with positive pathology in one. The three remaining patients were clinically observed, including one with HPV-positive disease who declined a neck dissection and subsequently suffered regional recurrence. Our current practice is to recommend a neck dissection if an equivocal or positive nodal scan fails to convert to a complete response on the second-look PET-CT.

There is limited other data exploring the accuracy of a second-look PET-CT. Liu et al. [18] reported on a series of 41 patients with HPV-associated oropharyngeal carcinoma and an equivocal or partial nodal response on initial PET-CT 12 weeks post chemoradiotherapy. A repeat PET-CT was performed after a further 16 weeks. Similar to our experience, there was a 71% conversion rate to a complete response and a high NPV of 97%. The authors recommended the use of repeat PET-CT to spare patients from unnecessary neck dissection. Vainshtein et al. [7] also reported on patients with HPV-related oropharyngeal carcinoma and serial surveillance. 21/22 (95%) and 12/12 (100%) of patients with an incomplete response at the primary site and nodes respectively on initial 3-month PET-CT assessment converted to a complete response on subsequent surveillance PET-CT.

Limitations of this study include the selection of the patients for the second-look PET-CT. There was no institutional protocol to guide this decision and it was based upon the “real world” opinion of the MDT/treating clinicians based on imaging and clinical findings. The rationale for the second-look PET-CT was uncertainty regarding response based upon clinical assessment and PET-CT. All second-look PET-CT scans were performed after an either equivocal or positive initial PET-CT based upon metabolic activity; this study does not inform on the value of repeated PET-CT in the context of a residual metabolically inactive residuum. Comparison between PET-CT response studies is challenging due to the lack of consensus regarding the optimal ‘scoring’ system [24; 27; 28]. There is considerable variation in what can be considered to be a ‘positive’ scan with series using a stricter definition reporting higher PPVs [14]. In routine practice we have used a similar semi-quantitative approach to reporting PET-CT scans [8; 18]. The cases in our analysis are predominantly oropharyngeal carcinoma. The value of a second-look PET-CT in non-oropharyngeal or HPV-negative oropharyngeal disease remains uncertain.

In conclusion, our results suggest the majority of patients who undergo a second-look PET-CT will convert to a complete response. This suggests that decisions regarding surgical intervention could be deferred until after the repeat scan, sparing many patients the need for intervention.

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Figures

Figure 1. Examples of patients with incomplete response on response assessment FDG PET-CT with conversion to complete response on second-look PET-CT in primary site (A) and lymph node (B). A). T3 N2c MO (TNM7) p16+ve base of tongue squamous cell carcinoma; SUV_{max} at baseline in primary site 13.1, response assessment 6.3 and complete response on second-look PET-CT. B). T0 N2a M0 (p16 unknown); SUVmax in necrotic lymph node at baseline 13.0, response assessment 3.1, complete response on second-look PET-CT (physiological uptake present in right masseter).

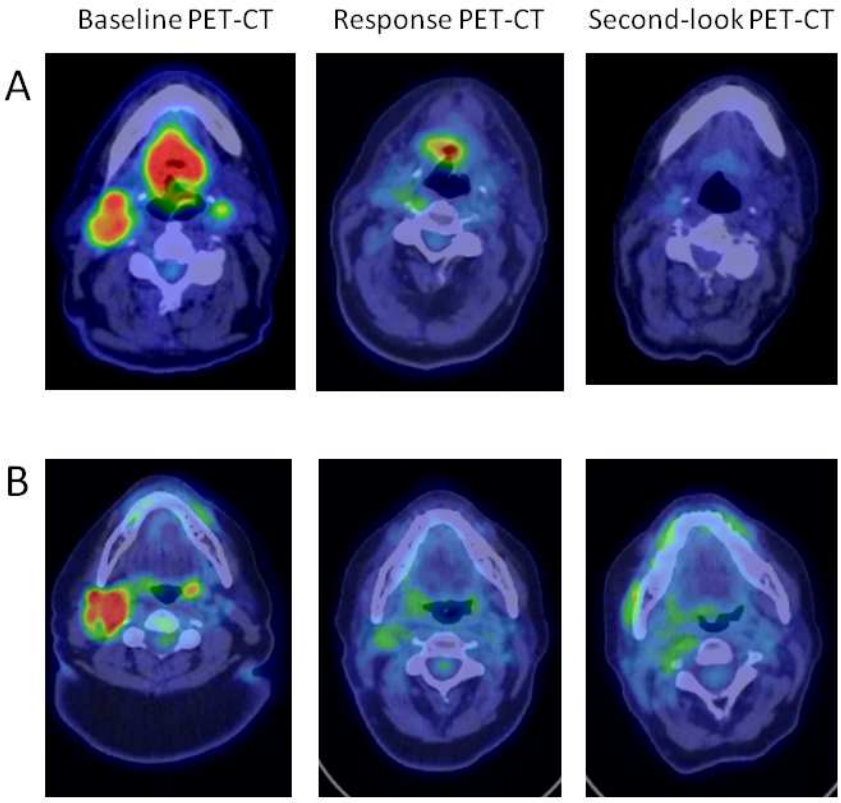
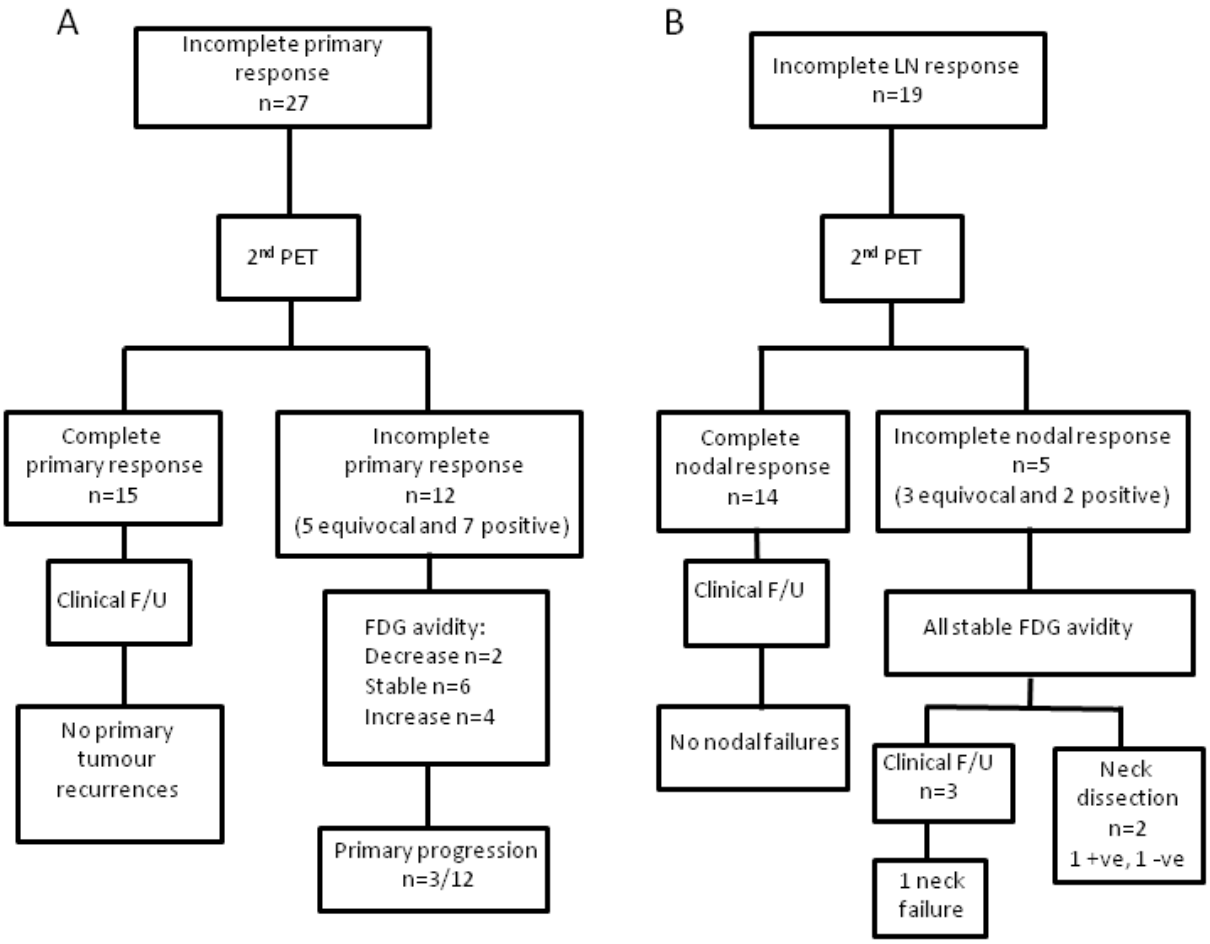


Figure 2. Flow diagrams summarising A) Patients undergoing second-look FDG PET-CT with uncertain primary tumour response on initial response assessment PET-CT. 1B) Patients undergoing second-look PET-CT with uncertain lymph node response on initial response assessment PET-CT.



Tables

Table 1: Patient, disease and treatment details of patients who underwent response assessment PET-CT (n=562) and of the subgroup who underwent a second-look PET-CT scan (n=40).

Characteristics		**1st PET response (total 562) n (%)**	**2nd -look PET response (total 40) n (%)**
Age	Median (range)	58 (24-84)	61 (45-76)
Gender	Male	423 (75)	27 (68)
	Female	139 (25)	13 (32)
Smoking	Smoker	205 (36)	12 (30)
	Ex-smoker	176 (31)	13 (33)
	Never Smoked	149 (7)	14 (35)
	Not recorded	32 (6)	1 (3)
Tumour site	Paranasal Sinus	9 (2)	0 (0)
	Oral Cavity	7 (1)	0 (0)
	Oropharynx	397 (71)	34 (85)
	Hypopharynx	53 (9)	2 (5)
	Larynx	48 (9)	2 (5)
	Unknown	48 (9)	2 (5)
Grade	Well Differentiated	7 (1)	0 (0)
	Moderate Differentiated	118 (21)	10 (25)
	Poorly Differentiated/ Basaloid	364 (65)	24 (60)
	Undifferentiated	6 (1)	0 (0)
	Not recorded	67 (12)	6 (15)
HPV status	Positive	228 (40)	24 (60)
	Negative	55 (10)	4 (10)
	Not recorded	279 (50)	12 (30)
T stage	T0	47 (8)	2 (5)
	T1	101 (18)	9 (23)
	T2	188 (34)	11 (28)
	T3	120 (21)	7 (18)
	T4	106 (19)	11 (28)
N stage	N0	81 (14)	5 (13)
	N1	61 (11)	3 (8)
	N2a	42 (8)	3 (8)
	N2b	274 (49)	22 (55)
	N2c	99 (18)	7 (18)
	N3	5 (1)	0
Stage	I	4 (1)	0

	II	24 (4)	3 (8)
	III	80 (14)	3 (8)
	IV	454 (81)	34 (85)
Use of chemotherapy	ICT CRT Cisplatin Cetuximab RT only	38 (7) 424 (75) 393 31 138 (25)	1 (3) 33 (83) 28 5 7 (18)

ICT=induction chemotherapy, CRT=chemoradiotherapy, RT=radiotherapy

Table 2: First response assessment PET-CT: summary of response categories (in patients who subsequently had second look PET-CT, n=40)

			Lymph node response		
		Total	**CR**	**Eq**	**Positive**
Primary Tumour response	**Total**	40	21	10	9
	CR	13	0	6	7
	Eq	19	14	4	1
	Positive	8	7	0	1

CR=complete response, Eq=equivocal response

Table 3: Second look PET-CT: summary of response categories (n=40)

			Lymph node response		
		Total	**CR**	**Eq**	**Positive**
Primary Tumour response	**Total**	40	35	1	4
	CR	28	24	1	3
	Eq	5	4	0	1
	Positive	7	7	0	0

CR=complete response, Eq=equivocal response

Table 4: Second-look PET-CT: response categories and disease outcomes

2nd look PET-CT result	**Disease +ve**	**Disease -ve**	**PPV/%**	**NPV/%**
	Primary tumour			
CR	1	27	4	96
Eq	0	5	0	100
Positive	3	4	43	57
	Lymph nodes			
CR	0	35	0	100
Eq	1	2	33	67
Positive	1	1	50	50

CR=complete response, Eq=equivocal response, PPV=positive predictive value, NPV=negative predictive value