ORIGINAL ARTICLE



CLINICAL IMPACT OF, AND PROGNOSTIC STRATIFICATION BY, F-18 FDG PET/CT IN HEAD AND NECK MUCOSAL SQUAMOUS CELL CARCINOMA

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Abstract: Background. The aim of this study was to determine prospectively the incremental value of positron emission tomography/computed tomography (PET/CT) over conventional assessment (clinical examination and CT/MRI imaging).

Methods. All patients undergoing ¹⁸F-fluorodeoxyglucose (FDG)-PET/CT for primary head and neck mucosal squamous cell carcinoma between January 2002 and December 2003 (inclusive) were included in this study provided they had undergone contemporaneous conventional assessment of the head and neck region and had 12 months minimum follow-up.

Results. Seventy-six patients underwent 100 PET/CT scans. The majority of patients (74%) were treated with definitive (chemo)-radiotherapy. Median follow-up time was 28 months. PET/CT led to a TNM classification alteration in 34% (12/35), a change in radiotherapy planning technique and/or dose in 29% (10/35), and altered treatment response assessment in 43% (13/30). A complete metabolic response was predictive of overall survival (p = .037).

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Conclusion. Our results support incorporation of PET/CT into the management paradigm of head and neck mucosal squamous cell carcinoma. © 2007 Wiley Periodicals, Inc. Head Neck 29: 986–995, 2007

Keywords: PET; CT-PET; head and neck; squamous cell carringma

Positron emission tomography (PET) with the glucose analogue, ¹⁸F-fluorodeoxyglucose (FDG), is a valuable tool with a rapidly expanding role in general oncology. ^{1–10} Our group and others have published on the utility of PET in head and neck mucosal squamous cell carcinoma (HNSCC). ^{11–18}

FDG-PET is an excellent functional imaging modality but has inherent anatomical limitations. The development of single-unit PET/CT scanners has addressed this limitation. In general oncology, PET/CT has been shown to significantly reduce

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the number of equivocal interpretations and improve diagnostic accuracy of lesion localization when compared with PET alone or PET and anatomical imaging performed independently. In head and neck cancer, PET/CT has also been shown to have improved diagnostic performance over PET alone. ^{19–22}

This study was designed when the first dedicated PET/CT scanner began clinical operation at Peter MacCallum Cancer Centre (PMCC) in January 2002. The aim of the study was to prospectively determine the incremental value of a PET/CT scan over standard assessment (clinical examination and CT/MRI imaging), in 3 clinical scenarios: staging, posttreatment assessment of response, and ongoing follow-up of HNSCC.

MATERIALS AND METHODS

Eligibility. All patients undergoing FDG-PET/CT for primary HNSCC between January 2002 and December 2003 (inclusive) were included in this study provided they had undergone contemporaneous conventional assessment of the head and neck region at PMCC and had a minimum follow-up of 12 months after the PET/CT scan. Patients with nasopharyngeal cancer were excluded because the natural history, therapeutic responsiveness, and treatment strategies are considerably different from SCC of the head and neck.

The study protocol was approved by the PMCC institutional ethics committee, and written informed consent was obtained from all participants.

Conventional Assessment. All patients underwent clinical assessment by a surgeon and/or radiation oncologist experienced in the management of head and neck cancer. This included history, physical examination, and fiberoptic endoscopy (where relevant). Ninety-three percent (93/100) of PET/CT scans were performed in association with conventional radiologic assessment with either a CT or MRI of the head and neck region. In each patient, the conventional assessment (prospectively determined prior to PET/CT) was based on all available clinical and radiological data.

PET/CT Protocol. Each patient underwent a combined PET/CT scan incorporating the neck, thorax, abdomen, and pelvis using an integrated PET/CT scanner (Discovery LS, GE Medical Systems, Milwaukee, WI).

As this study evaluated the incremental rather than the independent value of PET/CT, the results were read, as in routine clinical practice, in concert with all available information at the time of evaluation including prior CT or MRI results.

The PET/CT scans were grouped into 3 clinical categories:

- 1. Those performed to assist in decision making regarding the definitive treatment for initial disease (*Staging PET/CT*).
- 2. Those performed following definitive treatment to assess for response (*Response Assessment PET/CT*)
- 3. Those performed after definitive treatment either for suspected recurrence or ongoing surveillance (*Follow-up PET/CT*).

In the posttreatment setting, the accuracy of PET/CT in detecting locoregional disease was determined by cytology/histology and/or clinical and radiologic follow-up. A true positive was assigned if disease was confirmed within 3 months; a false positive, if there was no confirmation at the site within 3 months. A true negative was assigned if there was no clinical/radiologic progression within 12 months or if a pathologically negative resection specimen was obtained; a false negative, if disease was confirmed within 12 months.

Clinical Impact of PET/CT. A requirement of the PET/CT clinical request form was prospective documentation of the patient's TNM classification and the intended management plan. The request form, shown in the Appendix, also captured the details of treatment intent and treatment modality.

For those patients undergoing Staging PET/CT, the anticipated radiotherapy (RT) dose and treatment technique were documented prospectively. In cases in which this was not clearly stated, then the pre-PET/CT treatment plan was deemed to have been according to standard protocols in our unit.

The post- PET/CT TNM classification, treatment intent, treatment modality, and RT technique and dose (for Staging PET/CT patients) were obtained by review of the patient's case history and RT planning documentation.

Clinical impact was considered "high" if PET/CT changed the treatment modality, "medium" if treatment modality was unchanged but RT planning technique or dose was altered, and "low" if there was no change in treatment modality or intent.

Statistical Methods. All eligible patients were included in the statistical analyses. A study close-

Table 1. Disease and treatment characteristics at initial presentation.

Patient characteristic	No. (%)	
Stage at presentation		
Ī	8 (11)	
II	7 (9)	
III	15 (20)	
IV	45 (59)	
Unknown*	1 (1)	
Primary tumor site		
Oropharynx	40 (53)	
Larynx	19 (25)	
Oral cavity	9 (12)	
Hypopharynx	4 (5)	
Nasal cavity	1 (1)	
Unknown primary	3 (4)	
Management of initial disease		
Definitive (chemo)radiation	56 (74)	
Surgery alone	9 (12)	
Surgery and postop (chemo)radiation	8 (11)	
Induction chemo → chemoradiation	1 (1)	
Palliative radiotherapy	2 (3)	

*Patient presented with recurrent disease 10 years after initial diagnosis—initial staging was not determinable.

out date of February 16, 2005, was chosen for the time-to-event analyses with survival times of living patients censored at this date.

The baseline characteristics were summarized using descriptive statistics. The Kaplan–Meier method was used to estimate overall survival from date of pathologic diagnosis. The median follow-up time was estimated using the reverse Kaplan–Meier method.

The percentages of patients having a change in treatment intent and/or modality, and a change in RT technique and/or dose, were calculated together with the 95% confidence intervals (CIs). The percentage of patients having a change in response assessment was calculated together with the 95% CI. Accuracy was assessed by computing the number of false-positive and false-negative cases.

The Kaplan-Meier method was used to estimate overall and disease-free survival from date of pathologic diagnosis, and the difference

between those patients with and without a complete metabolic response was tested using the Mantel-Cox log rank test.

Statistical analyses were performed using S-plus 2000 Professional (MathSoft, Seattle, WA, 1999) and StatXact 6.0 (Cytel Software Corporation, Cambridge, MA, 2003) software.

RESULTS

Seventy-six patients were eligible for inclusion and underwent a total of 100 PET/CT scans. The median follow-up time from date of pathologic diagnosis was 28 months (95% CI, 27–33 months). Two patients were lost to follow-up 836 and 845 days after diagnosis. The median age at diagnosis was 59 years (range, 21–83 years), and 70% (53/76) were male. The overall survival for all patients was 81% at 2 years (95% CI, 70% to 88%).

Disease and treatment characteristics are summarized in Table 1.

Staging PET/CT. Thirty-five patients underwent a staging PET/CT scan. All were conventionally assessed with CT (34/35) and/or MRI (8/35) as well as clinical examination.

Staging Changes Resulting from PET/CT. Twelve (12/35) patients (34%) had a change in TNM classification as a result of PET/CT (95% CI 19% to 52%). Two patients had disease downstaged from N2c to N1 and N2c to N2b. Ten patients had disease upstaged: 1 in T classification (T0 to T1), 8 in N classification (4 from N2b to N2c, 2 from N2a to N2b, and 1 each N0 to N2c, N1 to N2b), and 1 in M classification (M0 to M1).

Clinical Impact. Staging PET/CT had high impact in 4/35 patients (11%) and medium impact in 10/35 patients (29%). The alterations in RT planning techniques and/or dose as a result of staging PET/CT are summarized in Table 2. Figure 1 depicts an example in which nodal upstaging by PET/CT resulted in a change in RT technique.

Table 2. Impact of staging PET/CT on radiotherapy technique/dose.					
Incremental effect of PET/CT	Change in radiotherapy dose/technique	No. of patients			
Nodal upstaging	Conformal parotid-sparing → parallel-opposed fields	1			
Contralateral nodes excluded	Parallel-opposed → conformal unilateral technique	1			
Nodal or primary upstaging	Increase in high-dose volume (receiving 60-70 Gy)	7			
Nodal downstaging	Reduction in volume receiving 66 Gy	1			

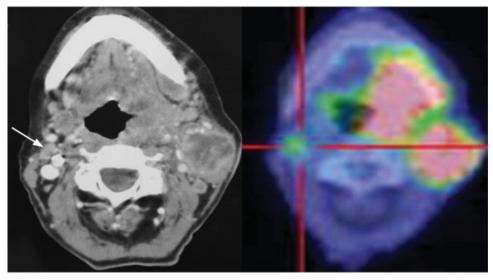


FIGURE 1. In this patient, conventional staging showed a T4N2b SCC L oropharynx. The R neck level II neck node (arrow) was not considered suspicious by CT criteria. PET/CT identified uptake at this site, upstaging the disease to N2c. This resulted in an alteration in technique from a conformal parotid sparing approach to parallel opposed fields.

Accuracy. Assessment of the accuracy of staging PET/CT for locoregional disease in our cohort was not possible as most patients received definitive RT or chemoradiation (30/35) and histopathologic confirmation of the PET result was not commonly obtained (including the patient upstaged from T0 to T1 where attempt at biopsy proved difficult and was unsuccessful). RT plans were altered on the basis of staging PET/CT and there is no mechanism for determining the accuracy of those alterations.

Response Assessment PET/CT. Thirty patients underwent a PET/CT to assess response to treatment. Ninety-three percent (28/30) underwent conventional radiologic assessment (within a median 3 days of PET/CT). The other 2 patients, both with T3 N2b oropharyngeal SCC, were conventionally assessed by clinical examination alone.

All patients had RT as part of their treatment, 28/30 (93%) had definitive and 2/30 (7%) postoperative RT. PET/CT was performed at a median time of 3.2 months posttreatment (range, 1.4–6.4 months).

Changes in Response Assessment Resulting from PET/CT. Overall, response assessment PET/CT altered the assessment of locoregional response in 13/30 patients (43%; 95% CI, 25% to 63%).

At the primary site, 8/30 (27%) had altered response assessment on PET/CT versus conventional assessment alone. Six patients had a partial

response (PR) on conventional assessment but complete metabolic response on PET/CT, and all of these were true negative (clinical/radiologic follow-up). The 2 patients who had a complete response (CR) on conventional assessment but only a partial metabolic response on PET/CT were both false positive (biopsy proven).

At nodal sites, there were 10/30 patients (33%) who had altered response assessment on PET/CT versus conventional assessment alone. Eight patients had a PR on conventional assessment but a complete metabolic response on PET/CT. All of these were true negative (1 pathologically proven and 7 on failure of progression). An example of 1 of these patients is depicted in Figure 2. One patient had a CR according to conventional imaging but partial metabolic response on PET/CT (true positive). One patient with a CR on conventional assessment and partial metabolic response on PET/CT died of unknown cause within 3 months without documentation of his true neck node status.

Clinical Impact. Impact was high in 11/30 patients (37%). Seven patients with negative neck scans were able to avoid unnecessary neck dissections. Of the remaining 4, one with PET/CT-detected distant metastatic disease avoided futile salvage neck dissection, 1 with suspected unresectable residual neck disease that was non-FDG avid avoided systemic chemotherapy, 1 with suspected

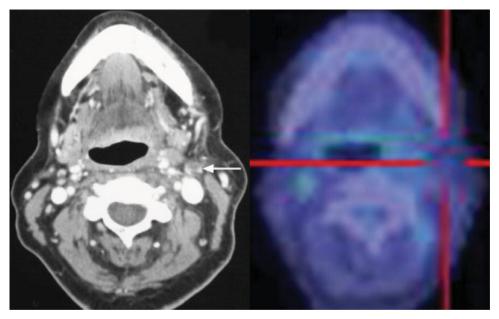


FIGURE 2. On the posttreatment CT, there was a residual enlarged cervical node, posterosuperior to L submandibular gland—measuring 12 × 8 mm (arrow). The pre- PET/CT plan was for neck dissection. The PET/CT fails to show any FDG avidity in the area of interest. This patient was therefore observed and remains alive and disease free at last follow-up.

residual tonsillar disease (non-FDG avid) avoided examination under anesthesia and biopsy, and the final patient underwent earlier salvage surgery for persisting FDG-avid, nasal cavity disease.

Accuracy was determined either by clin-Accuracy. ical follow-up and/or pathologic confirmation. All 21/30 scans that were negative for residual locoregional disease were true negative (100% negative predictive value [NPV]). There were 4/30 false positives at the primary site (43% positive predictive value [PPV]) and 3/30 at nodal sites (50% PPV). Of the false positives at the primary site, 2 led to a change in response assessment as previously described. The other 2 were concordant with conventional assessment of residual disease but did not progress clinically with ongoing follow-up. At nodal sites, 1 false positive was a reactive node in response to a localized infection (resolved clinically with resolution of the infection); the other 2 were both reported as "suggestive" of residual disease; however, both failed to progress on followup. These false-positive PET/CT scans were performed at 1.3 to 4.3 months posttreatment. There were no false negatives for locoregional disease.

At distant sites, there was 1/30 false negative in a patient who developed metastatic lung dis-

ease 10 months after his PET/CT. He did not undergo conventional imaging of his chest at the time of PET/CT and remained in locoregional control at the time of distant relapse.

Survival vs Metabolic Response. Figures 3 and 4 demonstrate the disease-free and overall survival for

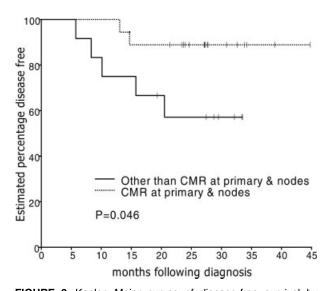


FIGURE 3. Kaplan–Meier curves of disease-free survival by response assessed on PET/CT. Patients with censored times are shown by tick marks. CMR, complete metabolic response.

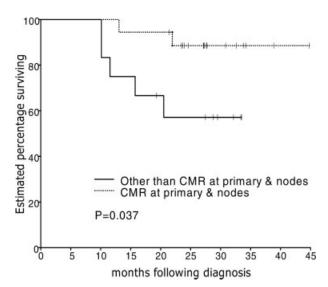


FIGURE 4. Kaplan–Meier curves of overall survival by response assessed on PET/CT. Patients with censored times are shown by tick marks. CMR, complete metabolic response.

those patients who had a complete metabolic response on PET/CT versus those who did not. There was a significant difference between the 2 groups for both disease-free survival (p = .046) and overall survival (p = .037).

Follow-up PET/CT. Thirty-five follow-up PET/CT scans were performed in 30 patients at a median time of 6.6 months post radical treatment (range, 1.6–166 months). Twenty-eight of these were for suspected recurrent disease and 7 were routine surveillance scans.

Eighty-six percent of scans (30/35) were performed in association with conventional radiologic assessment. The remaining 5 cases were conventionally assessed by clinical examination alone.

Clinical Impact. Impact was high from 12/35 scans (34%). Three patients were able to avoid examination under anesthesia and biopsy of the primary site. Four patients avoided salvage surgery for suspected locoregional recurrence, when PET/CT confirmed distant metastatic disease in 2 and excluded neck recurrence in 2. Two patients had second primaries detected that were able to be treated radically. One received adjuvant RT to his resected axilla when PET/CT excluded other sites of metastatic disease, and 1 underwent further investigation of lung lesions identified as suspicious on PET/CT. One patient's treatment intent became curative

instead of palliative when PET/CT excluded lung metastases. The final patient had unfortunately already undergone salvage laryngectomy before PET/CT revealed metastatic lung cancer.

In 2 patients, false findings on PET/CT led to changes in management. One underwent invasive investigation for false-positive uptake in the larynx. Another patient had an equivocal left lung lesion on PET/CT (suspicious on CT) and did not undergo biopsy at the time but progressed to develop metastatic pulmonary disease within 12 months.

Accuracy. Accuracy was determined either by ongoing observation and/or pathologic confirmation. True positives were recorded in 5/35 scans at the primary site and 8/35 scans in the neck. There were 4/35 true-positive scans for metastatic disease and a further 4 for second primary cancers. There were 3/35 false-positive scans at the primary site (63% PPV); 2 were in the same patient who had a persistent, biopsy negative vallecular ulcer, and the other was in a patient who had uptake in the oropharynx but failed to progress at this site. There was 1/35 false positive at a nodal site, proven negative on subsequent neck dissection (89% PPV).

There was only 1/35 false negative scan for locoregional disease—this patient developed neck recurrence 4 months after his PET/CT (96% NPV).

At distant sites, there were 7/35 false negatives in patients who developed metastatic disease within 12 months. Five of the 7 cases had progressed with uncontrolled locoregional disease when they developed distant metastases. The 2 that remained in locoregional control developed overt metastatic lung disease 9 and 11 months, respectively, after the negative scan.

DISCUSSION

PET/CT offers the advantage of combining anatomic and metabolic data, compared with PET, which provides functional imaging data only. There are data supporting the superiority of PET/CT over PET alone in general oncology. PET/CT has been shown to be of particular benefit in improving the characterization of equivocal lesions and also in determining the exact anatomical location of abnormal FDG uptake. ^{20,23,24}

In head and neck cancer, PET/CT should be of even greater value given the complex anatomy and the presence of multiple normal structures with variable intensity FDG uptake (e.g., lymphoid tissue, salivary glands, and muscles). 19

A small number of studies have compared PET versus PET/CT in head and neck cancer. Schoder and colleagues found PET/CT more accurate in localizing abnormalities, particularly in areas previously treated with surgery or RT and also in reducing the fraction of equivocal lesions. ²¹ The clinical impact of PET/CT compared with PET alone was reported but not its impact compared with conventional assessment alone. Others have also found PET/CT to be superior to PET alone in improving radiologist confidence and accuracy in head and neck malignancy. ^{22,25}

Our study of 76 patients with a median followup of 28 months is the first to prospectively assess the incremental clinical impact of PET/CT over conventional clinical and radiological assessment in HNSCC. Staging PET/CT led to a TNM classification change in 34%, most commonly owing to nodal upstaging. Clinical impact was medium with an alteration in RT planning technique or dose in 29%. However, because treatment plans were altered on the basis of the PET/CT findings and may thereby have altered the course of disease, their accuracy could not be validated.

PET/CT had high clinical impact when performed in addition to standard clinical assessment in the settings of assessment of posttreatment response and ongoing follow-up. Response assessment PET/CT was reliably accurate in excluding residual locoregional disease and led to a 37% change in either treatment modality and/or treatment intent. The absence of false negatives for locoregional disease in posttreatment evaluation supports the use of PET/CT to determine patients in whom ongoing observation rather than surgical intervention is appropriate and safe management.

It is well documented that the probability of obtaining a false-positive posttreatment PET scan decreases with time after completion of treatment, as treatment-induced inflammatory reactions heal. ^{16,26,27} Protracted healing of radiation reactions, secondary infection, or ongoing irritation due to smoking might all be expected to increase the false-positive rate. Most authors recommend 8 to 12 weeks as the optimal time for response assessment. ^{16,18,26,28} Clearly, a compromise needs to be struck between the risk of a false positive and the risk of delaying appropriate salvage intervention.

We believe that 3 months is an appropriate time for performing the posttreatment PET/CT.

For patients with a complete clinical, radiological, and metabolic response at that time, ongoing regular (3 monthly) clinical follow-up is recommended. In patients with high-risk disease, e.g., N3 nodal disease, a repeat PET/CT at 6 months is performed. If there is a complete metabolic response at 3 months but a clinical or radiological abnormality persists, close clinical assessment (6 weekly) and a repeat PET/CT in 3 months is recommended. A negative PET/CT could allow ongoing regular (3 monthly) clinical follow-up, with a further PET/CT at 12 months posttreatment.

False-positive results were more common in this series (13% at the primary and 10% at nodal sites) than we have previously reported using older stand-alone PET technology. ^{16,18} This probably reflects the higher spatial and contrast resolution of the current scanner allowing detection of more subtle regions of increased FDG uptake. This enhanced sensitivity would tend to increase the NPV but potentially decrease the PPV as observed in this study.

In the ongoing follow-up group, PET/CT had high impact in detecting distant metastatic disease and second primary cancers. These results support our previous study using stand-alone PET.¹⁸ However, some 20% of patients with a PET/CT negative for distant metastases went on to develop overt metastases within the next 12 months, most often in association with progressive locoregional disease. This is not surprising given that these metastases would have been only microscopic at the time of PET/CT or may even have seeded subsequent to the scan in patients with progressive locoregional disease.

CONCLUSION

We have demonstrated that PET/CT has a major incremental impact in the staging and posttreatment management of patients with HNSCC. PET/CT has a very high NPV for residual/recurrent locoregional disease in posttreatment evaluation, determining those patients in whom ongoing observation rather than surgical intervention is appropriate and safe management. Our results suggest addition of a posttreatment PET/CT scan into the patient's posttreatment management paradigm now constitutes optimal posttreatment care.

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PET Imaging Request Form - Oncology

PLEASE COMPLETE BOTH SIDES & ENSURE FORM IS SIGNED BY THE REFERRING CONSULTANT

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If a diad	Please ensure that all <i>previous films</i> are brought by the patient to their PET scan. If a <i>diagnostic CT</i> is required to coincide with the PET scan, this will require a separate CT request &				
booking to be made on Ph: 03 9656 1026 or Fax: 9656 1406.					

Version: 3-Feb-07 Page 1 of 2 Version: 3-Feb-07 DOB Page 2 of 2

Medicare rebates are available to private patients referred by a Specialist if the clinical indication meets the following criteria & the requisite information on this form is fully completed.

* Other Non-funded indications will attract a charge of \$800.00 or \$400.00 for Pension & Concession card holders. Overseas & Screening patients will attract a charge of \$1500.00 & are billed on the day of the scan.

INCOMPLETE REFERRALS WILL NOT BE BOOKED.

Please Select the appropriate clinical indication	on below & complete column appropriate to your selection.
Staging/Diagnosis	Restaging/Surveillance
 □ Solitary pulmonary nodule □ Staging of newly diagnosed NSCLC (LUNG CANCER) being considered for radical RT or surge 	Restaging of COLORECTAL carcinoma in patients being considered for resection of limited liver or pulmonary metastases
 □ BRAIN – primary tumour grading/biopsy guidance □ CERVICAL cancer staging prior to radiotherapy 	 Restaging of COLORECTAL carcinoma with clinical/structural suspicion of recurrence
 Staging of newly diagnosed OESOPHAGEAL cand being for radical RT or surgery 	Restaging of HEAD & NECK cancer Restaging of OVARIAN cancer
 Staging of newly diagnosed GASTRIC cancer being considered for surgery 	g BRAIN – primary tumour restaging. Recurrence or radiation necrosis.
□ Staging of newly diagnosed HEAD & NECK cancer	 Metastatic MALIGNANT MELANOMA with potentially-resectable disease
Evaluation of metastatic cervical nodes from UKPStaging of newly diagnosed LYMPHOMA	 Evaluation of residual mass after treatment of LYMPHOMA
 Metastatic MALIGNANT MELANOMA with potentially-resectable disease 	Restaging of suspected recurrent or residual LYMPHOMA
☐ Identification of biopsy site for SARCOMA	☐ Restaging of SARCOMA following definitive therapy
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Stage by Clinical &/or Investigation Findings Performed Up to Time of Referral T-stage Site: N stage Location: M stage Site(s):	to Time of Referral No evidence of disease Local recurrence Site: Systemic disease Site(s): Equivocal Location:
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What would your management plan be if PET were unavailable#; Surgery Radical radiotherapy Radical chemoradiation Radical chemoradiation -> Surgery Neoadjuvant chemotherapy-> Surgery Systemic chemotherapy Palliative radiotherapy Invasive biopsy Observation Other	What would your management plan be if PET were unavailable#; Salvage curative surgery Palliative surgery (debulking etc) Radical radiotherapy Radical chemoradiation Combined modality. Specify Systemic chemotherapy Palliative radiotherapy Expectant palliative Invasive biopsy Observation Other
Management Plan Intent ☐ Curative or ☐ Palliative	Management Plan Intent ☐ Curative or ☐ Palliative

Please note that the above information is vital to assessment of the impact of PET & the PET scan will not be booked until all this information is supplied. If you have any questions please feel free to contact us.

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