PET Changes Management and Improves Prognostic Stratification in Patients with Head and Neck Cancer: Results of a Multicenter Prospective Study

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The primary aim of this study was to determine the impact of PET in changing initial management plans in patients with untreated head and neck cancer. Secondary aims were to determine the incremental staging information provided by PET and to document the effect of PET on treatment outcomes. **Methods:** Patients with untreated head and neck cancer underwent PET scans. Pre-PET management plans were documented by referring clinicians unaware of the PET results, and management plan changes due to PET scan findings were documented. Follow-up to 12 mo after treatment was performed to determine actual management and clinical outcomes. **Results:** A total of 71 patients (median age, 56 y; 69% male) were studied. PET scans resulted in management change in 33.8% of patients. Moreover, PET was able to detect additional sites of disease in 39.4% of patients. Follow-up data showed that PET improved the classification of patients into curative and palliative categories. Trends toward inferior disease-free survival and lower complete response rates in patients with additional lesions detected on PET were demonstrated. In addition, a trend toward inferior disease-free survival in patients with a higher maximum standardized uptake value was shown. **Conclusion:** These data unequivocally demonstrate the significant impact of PET on management and outcomes in patients with untreated head and neck cancer.

Key Words: PET; head and neck cancer

PET using ^{18}F-FDG is widely employed in the initial staging of many tumors. Use of ^{18}F-FDG in in vivo cancer imaging is based on the observation of enhanced glycolysis in tumor cells. It is considered to be a highly sensitive technique but with variable specificity (1,2).

Several studies have evaluated the use of PET in the initial staging of head and neck cancer (3–13). ^{18}F-FDG PET may offer advantages over anatomic imaging in the assessment of primary tumors, as it can detect superficial or submucosal primary tumor infiltration without adjacent tissue deformation, and nodal disease (1,2). This is particularly useful in situations in which the anatomic imaging is equivocal and the disease is not assessable by direct visualization. In this respect, the role of ^{18}F-FDG PET is as an adjunct to currently available methods of staging. ^{18}F-FDG PET is particularly useful in the detection of cervical nodal metastases not identified by other imaging modalities (3,14).

Emerging evidence suggests that the intensity of head and neck tumor uptake on a PET scan as measured by the maximum standardized uptake value (SUV_{max}) correlates with clinical outcome (15).

However, conflicting data exist on the role of PET in detecting the primary lesion in patients with carcinoma of unknown primary presenting as nodal disease in the neck (16,17).

In untreated head and neck cancer, there is a lack of prospective multicenter studies examining the impact on management of PET. Moreover, to our knowledge, there have been no prior multicenter studies that have established the impact of PET on patient outcomes.

Our study, therefore, examined the use of PET in the initial staging of patients with carcinoma of the head and neck region, including those with carcinoma of unknown primary presenting with cervical nodal metastases. The main aim of our study was to determine the impact of PET in changing initial management plans. Secondary aims were to determine the incremental staging information provided by PET and to document the effect of PET on treatment outcomes.

MATERIALS AND METHODS

Patients

This prospective study was conducted at 3 Australian PET centers. Eligible patients had previously untreated carcinoma of the nasal cavity, nasopharynx, oral cavity, oropharynx, hypopharynx, or larynx, or had metastatic disease involving cervical lymph nodes from an unknown primary. Patients had to have an Eastern Cooperative Oncology Group performance status of less than or equal to 2 and had to be at least 18 y of age and available for follow-up for at least 12 mo after treatment. Patients were excluded if they had previously undergone surgical resection or radiation therapy for head and neck cancer, had concurrent active cancer, had symptomatic or radiologic evidence of distant metastatic disease, were receiving concurrent treatment with any other anticancer therapy, had uncontrolled diabetes mellitus, or were pregnant. The institutional ethics review boards at the participating hospitals approved the study, and informed consent was obtained from all patients. The study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1975.

Conventional Staging Procedures

All patients were to have undergone examination under anesthesia and biopsy to confirm the diagnosis. Contrast-enhanced CT of the neck was required within 6 wk of the PET scan. Depending on clinical suspicion, the referring clinicians performed MRI of the neck, CT of the chest and other regions, and chest radiography before PET. Pre-PET investigations were performed according to institutional protocols at the referring centers and were not standardized. Investigators were required to record if lesions seen on PET were adequately assessed by prior anatomic imaging methods.

PET Scan Procedure and Image Interpretation

Patients fasted for a minimum of 6 h before the PET study. ^{18}F-FDG at a dose of 120–440 MBq was administered intravenously. After a minimum uptake period of 45 min, PET emission data were acquired from the skull vertex to at least the lower abdomen. At sites with PET/CT scanners, CT scans were performed for the purposes of anatomic localization and attenuation correction of image data. PET transmission data were used for attenuation correction if the CT data were not available. Experienced, credentialed PET specialists with full knowledge of conventional imaging results interpreted the PET scans. Lesion interpretation was based on the final PET reports. SUV_{max} was measured for at least 1 lesion in a large subgroup of patients. SUV_{max} was calculated by measuring the maximum concentration of ^{18}F-FDG in a lesion and correcting for the body weight and injected dose of ^{18}F-FDG.

Documentation of Management Plans

Before receiving the results of the PET scans, the referring clinicians were required to document a management plan for the patient, as if PET findings were not available, but with access to all other clinical and conventional imaging results. This management plan outlined the modalities planned such as surgery, radiation therapy, chemotherapy, or a combination. Information was also collected on the planned extent of these therapies. After the release of the PET results, a second management plan was recorded, including any changes in intended management as a result of the PET scan findings. The actual implemented management plan, based on follow-up data, was also recorded.

Impact of PET on Patient Management

The impact of PET on patient management plans was assessed by comparing pre-PET management plans with post-PET management plans for individual patients and by asking the referring clinician if the management had been changed on the basis of PET results.

Patient Follow-up and Prediction of Disease-Free Survival on Basis of PET

Patients underwent follow-up for 12 mo after the completion of therapy. The date of tumor progression was recorded. Where possible, the results of posttreatment imaging were obtained. Clinicians were asked to assess the clinical response at 12 wk after the completion of therapy. The impact of detection of additional lesions by PET (when compared with conventional imaging) was analyzed for the effect on disease-free survival. The utility of SUV_{max} for predicting disease-free survival was also analyzed.

Statistics

A sample size of at least 60 patients was initially planned. This assumed that if 12 patients (20%) had data insufficient for analysis, and if 20% of the remaining patients were to have a change in management plan, the 95% confidence intervals would be 9%–31%. Bivariate tables were analyzed using the χ^2 test or Fisher exact probability test. Survival analyses were performed using the Kaplan–Meier method, and the groups were compared using the log-rank test.

RESULTS

Patient Demographics

Between December 17, 2003, and June 3, 2005, 72 patients were enrolled in the study. One patient was lost to follow-up before it could be confirmed that his treatment plan had been initiated. Thus, 71 patients were available for data analysis. The median patient age was 56 y (range, 35–86 y), 49 of whom were men (69%) and 22 of whom were women (31%). Tumor sites classified by ICD-10-AM code are shown in Table 1.

Lesions Detected on PET, Compared with Conventional Imaging

A total of 156 lesions were detected in the pre-PET evaluation. Not all of the pre-PET investigations were documented, as some did not show additional lesions beyond that seen on CT. Based on the documented investigations, all patients underwent a CT scan of the neck, although in 4 cases, the MRI results, rather than the CT results, were used for lesion documentation. Six patients underwent CT brain studies, 28 underwent a CT scan of other regions, 16 underwent an MRI, 8 underwent ultrasound, 6 underwent plain radiograph, and 16 had lesions documented on the basis of clinical examination. Lesion interpretation for the pre-PET investigations was based on radiology reports and information provided by referring physicians. In instances where multiple lymph nodes could not be easily separated from each other, that group was treated as 1 lesion. Primary lesions were detected in 56 patients, with 2 primaries identified in one case. The primary lesion was not detected in 15 patients.

TABLE 1
Tumor Classification for Individual Patients

Site (ICD-10-AM Code)	No. patients
Malignant neoplasm of base of tongue (C01)	6 (8.5%)
Malignant neoplasm of other and unspecified parts of tongue (C02)	6 (8.5%)
Malignant neoplasm of floor of mouth (C04)	4 (5.6%)
Malignant neoplasm of palate (C05)	2 (2.8%)
Malignant neoplasm of other and unspecified parts of mouth (C06)	1 (1.4%)
Malignant neoplasm of tonsil (C09)	9 (12.7%)
Malignant neoplasm of oropharynx (C10)	5 (7.0%)
Malignant neoplasm of nasopharynx (C11)	7 (9.9%)
Malignant neoplasm of pyriform sinus (C12)	2 (2.8%)
Malignant neoplasm of hypopharynx (C13)	4 (5.6%)
Malignant neoplasm of accessory sinuses (C31)	1 (1.4%)
Malignant neoplasm of larynx (C32)	9 (12.7%)
Secondary and unspecified malignant neoplasm of lymph nodes (C77)	15 (21.1%)
Total	71 (100%)

Forty patients (56.3%) were evaluated with stand-alone PET. Thirty-one patients (43.7%) underwent PET/CT scans.

PET detected 171 lesions. In 28 patients (39.4%), PET detected 43 additional lesions, 9 of which were primary lesions; 27 were regional lymph nodes, including instances of multiple lymph nodes in 1 location; and 7 were distant metastases. Of the 171 lesions detected on PET, 160 were interpreted as consistent with malignancy, and 11 lesions were equivocal.

Pre-PET evaluation did not detect a primary lesion in 15 patients. Seven of the primary lesions detected only by PET relate to 7 of these 15 patients (46.7%). The other 2 additional primaries detected on PET were second primaries detected in 2 patients in whom the first primary lesion had been detected before PET. Figure 1 shows an example of a primary lesion detected on PET.

In 15 patients (21.1%), 28 lesions were detected on the pre-PET evaluation but not detected on PET. Of these 28 lesions, 5 were primary lesions, 22 were regional lymph nodes, and 1 was a possible distant metastatic lesion. Most of these lesions (18) were detected on the CT scan. The remaining 10 were detected on 1 or more modalities other than CT (MRI, biopsy, clinical examination). All 15 patients had CT scans before PET. In 2 cases, surgical biopsies performed between the pre-PET evaluation and the PET scan resulted in lesions not being detected on PET. In one case, a localized cervical lymph node was excised, and in the other, only a primary lesion (left tongue) was detected before the PET scan and this was excised before the PET scan.

The American Joint Committee on Cancer TNM stage was documented on the basis of the pre-PET evaluation and again after the PET scan. Overall, TNM stage was altered in 22 patients (31%). Six patients (8.5%) had a change in T stage based on PET (1 upstaged, 1 changed to stage TX [primary stage not assessable], and 4 changed from TX). Fourteen patients (19.7%) had a change in N stage (9 upstaged, 3 downstaged, and 2 changed from NX [nodal stage not assessable]). Nine patients (12.7%) had a change in M stage (1 upstaged, 2 downstaged, and 6 changed from MX [distant metastases not assessable]).

Additional lesions were detected in 18 of 40 patients scanned using stand-alone PET and in 10 of 31 patients scanned with PET/CT. No significant difference between these groups (χ^2 test) was shown. Stand-alone PET detected 95 lesions in 40 patients (mean, 2.38); PET/CT detected 76 lesions in 31 patients (mean, 2.45). Management was changed in 12 patients (30%) in the stand-alone PET group and in 12 patients (39%) in the PET/CT group. This difference in management was not significant by χ^2 analysis (χ^2 = 0.27, $P = 0.60$).

Post-PET Change in Management Plan

Management plans were altered on the basis of the PET result in 24 patients (33.8%) (95% confidence interval,
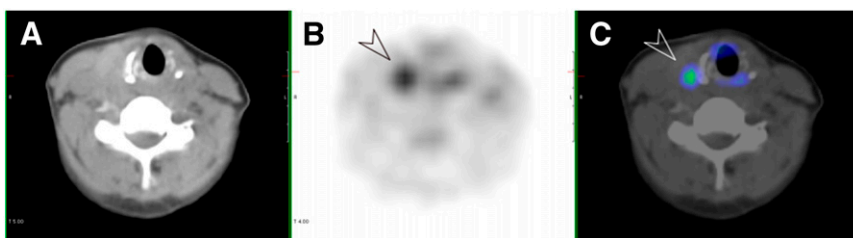
FIGURE 1. CT (A), PET (B), and combined PET/CT (C) images from a patient with metastatic cervical nodal disease of unknown primary. PET detected lesion in right lobe of thyroid gland (arrowhead). The patient was subsequently found to have primary thyroid cancer and went on to have thyroidectomy.

22.8%−44.8%). PET detected additional lesions in 19 of these 24 patients. In the other 5 patients, all of whom were treated with radiation therapy, the radiation volume was changed in 3, and the radiation dose was changed and chemotherapy abandoned in 2. An example of a patient whose radiation volume was changed is shown in Figure 2. The pre-PET and post-PET management plans and changes are shown in Table 2. Detailed information on the management plans for all patients before PET and after PET are outlined in Table 3.

Referring clinicians rated the impact of PET on patient management as high in 13 (18.3%), medium in 11 (15.5%), and low in 47 (66.2%). These results were significant by χ^2 analysis ($\chi^2 = 69.8$, $P < 0.001$).

Referring clinicians were also asked to record if the management plan intent was curative or palliative before PET and if a change on the basis of the PET results was warranted. The number of curative-intent patients remained similar, with 70 before PET and 65 after PET. Seven patients (9.9%) had treatment intent altered by PET (6 patients were changed from curative to palliative, 1 from palliative to curative).

Actual Treatment

At the 12-wk posttreatment follow-up, actual treatment was compared with the treatment planned after PET. This information was available for all 71 patients, including 53 whose actual treatment was as planned after PET (74.6%) and 18 whose actual treatment differed from that planned after PET (25.4%). Review of these 18 patients showed that in 17 cases, the actual treatment implemented was consistent with the PET results. In the majority, planned treatment was varied because of treatment-related toxicity, disease progression, or refinement of the management plan in light of the patient's response to initial treatment.

In only 1 case, the treatment was not consistent with the PET findings: a second primary lesion was identified at the time of surgery and an (unplanned) excisional biopsy of this left tongue lesion was performed. Neither PET nor CT had identified this lesion. Thus, actual treatment was consistent with PET findings in almost all patients.

Posttreatment Clinical Response

Patients were also grouped according to clinical response at 12-wk after treatment and to whether the pretreatment PET scan did or did not detect additional lesions.

Patients who had additional lesions seen on PET were less likely to achieve a complete response as judged by the referring clinician (59%) than those with no additional lesions (76%). To generate adequate numbers for statistical analysis, the noncomplete responders were combined and compared with the complete responders. The result was not significant ($P = 0.18$, Fisher exact probability test).

Disease-Free Survival

At 12-mo follow-up, disease-free survival data were available for 64 patients (with 7 having been lost to follow-up or having died without progression being identified before 12 mo). These data demonstrated progression in 4 of the 4 available patients classified as palliative-intent after PET and in 20 of the 60 available patients classified as curative-intent after PET. This difference was statistically significant ($P = 0.017$, Fisher exact probability test).

The effect of additional lesions detected on PET was evaluated using a Kaplan–Meier survival analysis (Fig. 3). A trend toward poorer disease-free survival in those patients who had additional lesions detected on PET was demonstrated, although this did not quite achieve significance ($P = 0.06$, log-rank test). This analysis was performed on the 69 patients for whom disease-free survival data were available.

An evaluation of the prognostic value of SUV_{max} (a measure of the intensity of tumor uptake on PET) was also performed. In this analysis, the single-highest SUV_{max} measured from a patient's various lesions was used. Fifty-three patients had sufficient data to perform this analysis. In 42 cases, the SUV_{max} related to a primary lesion, and in 11, a lymph node region. Patients were divided into high- and low-SUV_{max} groups based on the median SUV_{max} of 6.5. The disease-free survival of the high- and low-SUV_{max} groups was compared with Kaplan–Meier survival analysis (Fig. 4). The analysis showed a clear trend toward poorer disease-free survival in the high-SUV_{max} group, although this did not achieve significance ($P = 0.13$, log-rank test).

DISCUSSION

This study demonstrates that PET has a significant impact on patient management and predicts outcomes in patients with previously untreated head and neck cancer. PET scans resulted in a clear management change in 24 of the 71 patients (33.8%). A high or medium management impact (treatment modality or intent changed because of PET, or
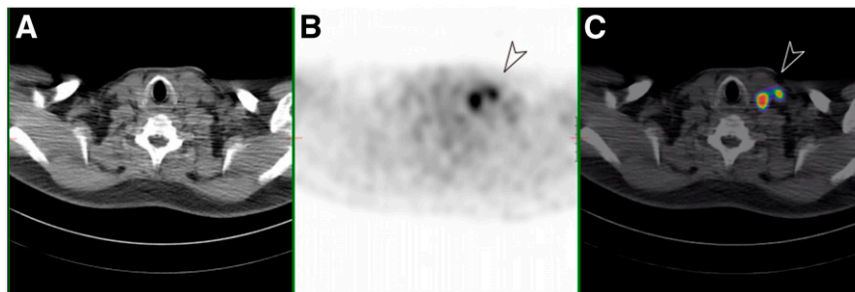
FIGURE 2. CT (A), PET (B), and combined PET/CT (C) images from patient in whom PET detected additional left supraclavicular nodal disease (arrowhead) that was not reported as pathologic on CT scan. This finding resulted in change in radiation target volume.

TABLE 2
Pre-PET and Post-PET Management Plans

Management Plan	Pre-PET plan All patients		Post-PET plan Management unchanged		Post-PET plan Management changed	
	n	%	n	%	n	%
Radiotherapy	15	21.1	10	14.1	6	8.5
Radiotherapy, then other (CT of chest and likely CT-guided biopsy of lung)	—	—	0	0.0	1	1.4
Surgery	9	12.7	5	7.0	1	1.4
Surgery, then other (core biopsy)	—	—	0	0.0	1	1.4
Surgery, then radiotherapy	10	14.1	7	9.9	4	5.6
Surgery, then chemotherapy, then radiotherapy, or Radiotherapy, then chemotherapy	3	4.2	2	2.8	1	1.4
Chemotherapy/radiotherapy (consecutive or concurrent)	32	45.1	22	31.0	10	14.1
Other (observation × 1, bronchoscopy × 1)	2	2.8	1*	1.4	0	0.0
Total	71	100.0	47	66.2	24	33.8

*Observation.

treatment modality or intent did not change although planned procedure, dose of therapy, or mode of delivery was altered because of PET, respectively) was also observed in a third of patients. Recently published data from the National Oncologic PET Registry in patients with a variety of cancers (particularly prostate, pancreas, and ovarian cancer) showed that intended management was changed in 36.5% of patients after PET (*18*). Prior single-institution retrospective studies in patients with head and neck cancer have also shown that PET scan results change management. The largest retrospective study of PET/CT was recently published and showed a management change in 31% of 123 patients (*19*). Other single-institution retrospective studies have also shown a management change in 18%–31% of patients with head and neck cancer (*20–22*). A recently reported single-institution prospective study of 35 newly diagnosed patients with head and neck cancer also reported management change in 40% of patients (*23*). Although a large proportion of patients in our study had stand-alone PET, rather than PET/CT, our results are of a similar magnitude. Our data represent, to our knowledge, the largest prospective and multicenter study conducted to date examining the impact of PET on the management of head and neck cancer.

PET was able to detect 43 additional lesions in 28 of the 71 patients (39.4%). PET did not identify a small number of primary tumors, most likely because of prior removal at biopsy or because the lesion was below the limits of resolution of any imaging modality (i.e., mucosal lesions seen at endoscopy). In 9 patients, primary lesions not previously known were identified; 2 patients had a second primary detected, and 7 of the 15 patients (46.7%) with unknown primaries and metastatic lymph node disease had primary tumors identified. The detection rate of unknown primaries in this series is higher than rates described by many literature reports (*16,17*) and may relate to the latest-technology PET scanners being used. In 4 of these 15 patients, additional regional lymph nodes were also identified, which illustrates the potential value of PET in this patient population.

Overall, TNM stage in 22 of the 71 patients (31.0%) changed. Although validation of sites of malignancy was not part of this trial design, the accuracy of PET in staging head and neck cancer has been extensively reported in the literature (*3–14,23*). Information from referring clinicians as well as from radiology and PET reports was used for lesion evaluation, and no centralized review of the imaging was made. Although this approach is a potential limitation of the study, the benefit of this method is that our results reflect actual clinical practice.

The detection of additional lesions was the principal contribution to management change, but alteration in radiation volume or dose was observed in 5 patients with no additional lesions detected on PET. Management intent (curative vs. palliative) was changed in a small number of patients after PET (9.9%), with 90.1% subsequently treated with curative intent, indicating the expected good prognosis of these patients.

The integration of PET into radiation therapy planning is an area of potential relevance for clinical practice (*24*). The high contrast between tumor and surrounding soft tissues on PET, when compared with CT or MRI, may improve the delineation of 3-dimensional radiation therapy target volumes (*25*). Although the impact of PET on target volumes was not an endpoint of our study, we did find that the radiation volume was altered in 3 patients in whom no additional lesions were detected on PET, indicating the potential impact of PET on radiation therapy even when it does not detect new sites of disease.

TABLE 3
Impact of PET on Detailed Patient Management Plans

Pre-PET plan	n	Post-PET plan	Impact	n
Radiotherapy	15	Radiotherapy	Treatment unchanged	10
		Radiotherapy, then chemotherapy	Chemotherapy added as second modality	1
		Radiotherapy, then chemotherapy	Chemotherapy added as second modality; change of intent from curative to palliative	1
		Radiotherapy	Radiotherapy course changed	1
		Radiotherapy	Radiotherapy course changed; change of intent from curative to palliative	1
		Radiotherapy, then other (CT of chest and likely CT-guided biopsy of lung)	Other added as second modality	1
Surgery	9	Surgery	Treatment unchanged	5
		Surgery, then radiotherapy	Radiotherapy added as second modality	1
		Radiotherapy	Radiotherapy instead of surgery; change of intent from curative to palliative	1
		Surgery, then radiotherapy, then chemotherapy	Radiotherapy + chemotherapy added	1
		Surgery, then other (core biopsy)	Other added as second modality	1
Surgery, then radiotherapy	10	Surgery, then radiotherapy	Treatment unchanged	7
		Surgery, then radiotherapy	Course of treatment changed	2
		Radiotherapy and chemotherapy	Chemotherapy added as a primary modality	1
Surgery, then chemotherapy and radiotherapy	2	Surgery, then chemotherapy and radiotherapy	Treatment unchanged	1
		Radiotherapy and chemotherapy	Surgery not performed	1
Surgery, then chemotherapy, then radiotherapy	1	Surgery, then chemotherapy, then radiotherapy	Treatment unchanged	1
Chemotherapy, then radiotherapy	3	Chemotherapy, then radiotherapy	Treatment unchanged	2
		Chemotherapy, then radiotherapy	Course of treatment changed	1
Radiotherapy and chemotherapy and other (±tirapazamine)	1	Radiotherapy and chemotherapy and other (±tirapazamine)	Course of treatment changed	1
Chemotherapy and radiotherapy	28	Chemotherapy and radiotherapy	Treatment unchanged	20
		Chemotherapy and radiotherapy	Course of treatment changed	4
		Radiotherapy	Chemotherapy abandoned; change of intent from curative to palliative	3
		Surgery, then radiotherapy	Chemotherapy abandoned, surgery added; change of intent from palliative to curative	1
Other (observation)	1	Other (observation)	Treatment unchanged	1
Other (bronchoscopy)	1	Surgery	Surgery instead of other	1
Total	71			71

Combined PET/CT scanners acquire coregistered PET and CT data in the course of a single scan. Several studies have addressed whether combined-modality PET/CT is superior to stand-alone PET in head and neck cancer staging, and PET/CT appears to have greater overall accuracy than does PET or CT alone (*26,27*). PET/CT, when compared with PET alone, reduces the number of equivocal lesions (*20*) and improves interobserver agreement (*28*). In our study, 43.7% of patients were imaged using PET/CT scanners. No significant difference between stand-alone PET and PET/CT was found for detection of additional lesions, number of lesions detected, or management change, although these comparisons were not planned study endpoints.

Follow-up analysis showed that actual treatment implemented was consistent with the PET findings in all but 1 patient. The detection of additional lesions on PET correlated with poorer disease-free survival and failure to achieve complete response, although these correlates did not quite reach statistical significance. The small number of patients who were classified as palliative after PET (having previously been planned to be treated with curative intent) had a significantly inferior disease-free survival. The intensity of uptake of PET as measured by SUV_{max} appeared to correlate with an inferior disease-free survival. Previous studies in untreated head and neck cancer have shown that SUV_{max} (*15*) and hypoxia detected on PET using the tracer fluoromisonidazole (*29*) are associated with disease-free survival. However, to our knowledge, ours is the first study to show that detection of additional lesions on PET and classification as a palliative patient after PET correlate with an inferior disease-free survival.

Some of the disease-free survival differences were possibly the result of management changes based on PET results, rather than improved prognostic stratification. However, to
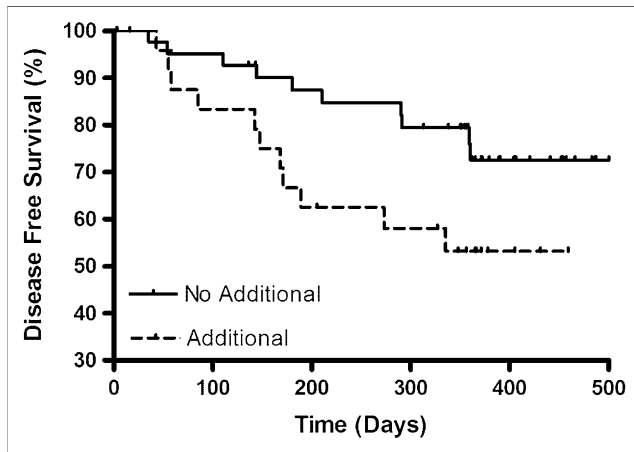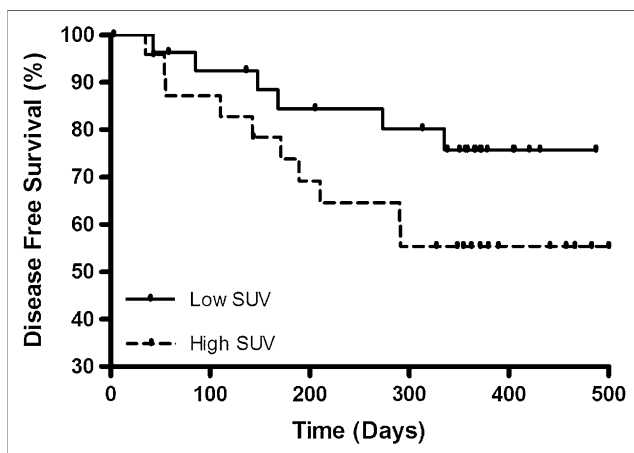
FIGURE 3. Kaplan–Meier analysis of disease-free survival in patients with additional lesions detected on PET vs. those with no additional lesions ($P = 0.06$, log-rank test). One patient who had follow-up data for more than 700 d was censored at 500 d for purposes of charting.

quantify this incorporation bias, either a much larger randomized study would have been required or referring physicians would have been required to ignore the PET scan results. Neither option was feasible in our population.

Different subgroups of head and neck cancer (base of tongue, oropharynx, etc.) are managed differently, and one limitation of the study was that the patient numbers in each of the subgroups were small, preventing individual analyses.

CONCLUSION

This prospective multicenter study clearly demonstrates that PET changes management plans and provides important prognostic information in a large proportion of patients with untreated head and neck cancer. PET also detects additional sites of disease and improves classification of patients into curative and palliative categories.

FIGURE 4. Kaplan–Meier analysis of disease-free survival in patients divided into high and low SUV groups ($P = 0.13$, log-rank test). One patient who had follow-up data for more than 700 d was censored at 500 d for purposes of charting.

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