RADIOLOGY—ORIGINAL ARTICLE

Fluorodeoxyglucose positron emission tomography/computerized tomography in differentiated thyroid cancer management: Importance of clinical justification and value in predicting survival

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Abstract

Introduction: The purpose of this study was to evaluate the added value of follow-up fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) to clinical assessment and predicting survival outcome in patients with differentiated thyroid cancers.
Methods: This is an institutional review board approved, retrospective study of 202 biopsy-proven thyroid cancer patients at a single tertiary centre. A total of 327 follow-up or surveillance PET/CT scans done 6 or more months from initial treatment completion were included in this study. Median follow-up from completion of primary treatment was 94 months (range, 6.17–534.1 months). Overall survival benefit was measured using Kaplan–Meier plots with a Mantel–Cox log-rank test. Multivariate Cox regression model is provided with clinical covariates.
Results: Of the 327 PET/CT scans from 202 patients, 161 were positive and 166 as negative for recurrence or metastasis. A total of 23 patients died during the study period. Patients with a positive PET/CT scan had shorter overall survival than those who had a negative scan ($P < 0.0001$, hazard ratio 6.1 (3.0–14.3)). In the context of clinical assessment, PET/CT identified recurrence in 50% (25/50) of scans without prior clinical suspicion and ruled out recurrence in 36.8% (102/277) of scans with prior clinical suspicion. In a multivariate Cox regression model, factors associated with overall survival were stage ($P < 0.0001$), time to scan ($P = 0.0005$) and PET/CT result ($P < 0.0001$).
Conclusion: FDG PET/CT performed in follow-up more than 6 months from primary treatment completion adds value to clinical judgment and a prognostic marker of overall survival in thyroid cancer patients.

Key words: differentiated thyroid cancer; follow-up; PET/CT.

Introduction

Thyroid cancer is one of the common endocrine malignancies and has gained special importance because of an observed increase in incidence over the last few decades all over the world.[1,2] This increase in incidence has been attributed to papillary thyroid cancer. However, the mortality of thyroid cancer has remained the same.[2] Thyroid cancers exhibit a range of histological variants, from the relatively less aggressive, differentiated thyroid cancers to the less favourable, aggressive, undifferentiated or anaplastic thyroid cancers. The prognosis and outcome of thyroid cancers vary across the different histological types. Papillary and follicular thyroid cancers have a relatively good prognosis with mortality rates less than 10%. However, almost one-third of these patients exhibit disease recurrence in their lifetime.[3]

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^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) has been found to have an increasing impact in the staging and follow-up of many human solid tumours, including thyroid cancers.[4–8] The role of FDG PET/CT has been established in differentiated thyroid cancer (DTC) lesions with negative radioiodine (RAI) uptake and elevated serum thyroglobulin (Tg).[9,10] The American Thyroid Association (ATA) has advised the use of FDG PET/CT in the localisation of disease in patients with DTC who have elevated Tg more than 10 ng/mL and a negative RAI whole body study. A multidisciplinary expert panel convened by the American Society of Clinical Oncology and the Society of Nuclear Medicine has also recommended the use of FDG PET/CT in the same context. However, the panel has not advocated the use of FDG PET/CT in the surveillance of these patients.[11] There has been considerable research evaluating the value of FDG PET/CT in the follow-up of differentiated thyroid cancer in the past.[12–16]

The objective of this study was to evaluate the prognostic value of follow-up FDG PET/CT on overall survival (OS) of patients with DTC and to estimate the added value of FDG PET/CT for clinical assessment at the time of the scan during follow-up.

Materials and methods

Eligible patients and follow-up

This was a retrospective study performed under a waiver of informed consent approved by the Institutional Review Board. The guidelines of the Health Insurance Portability and Accountability Act were followed. All patients treated for biopsy-proven DTC at a single tertiary centre with one or more follow-up FDG PET/CT scan performed at least 6 months from primary treatment completion were included in the study. Between March 2001 and January 2013, a total of 202 thyroid cancer patients met our study inclusion criteria providing a total of 327 follow-up PET/CT scans (range, 1–6 per patient). These scans were performed as part of clinical follow-up of DTC patients with history of elevated Tg and a negative RAI scan on follow-up (Fig. 1) or at the time of clinical concern for suspected recurrence by clinicians. All patients were followed until death or censored on the last day of follow-up at our institution. Median follow-up from completion of primary treatment was 94 months (range, 6.17–534.1 months). Patient demographics, histology, stage and other therapy details are summarised in Tables 1 and 2.

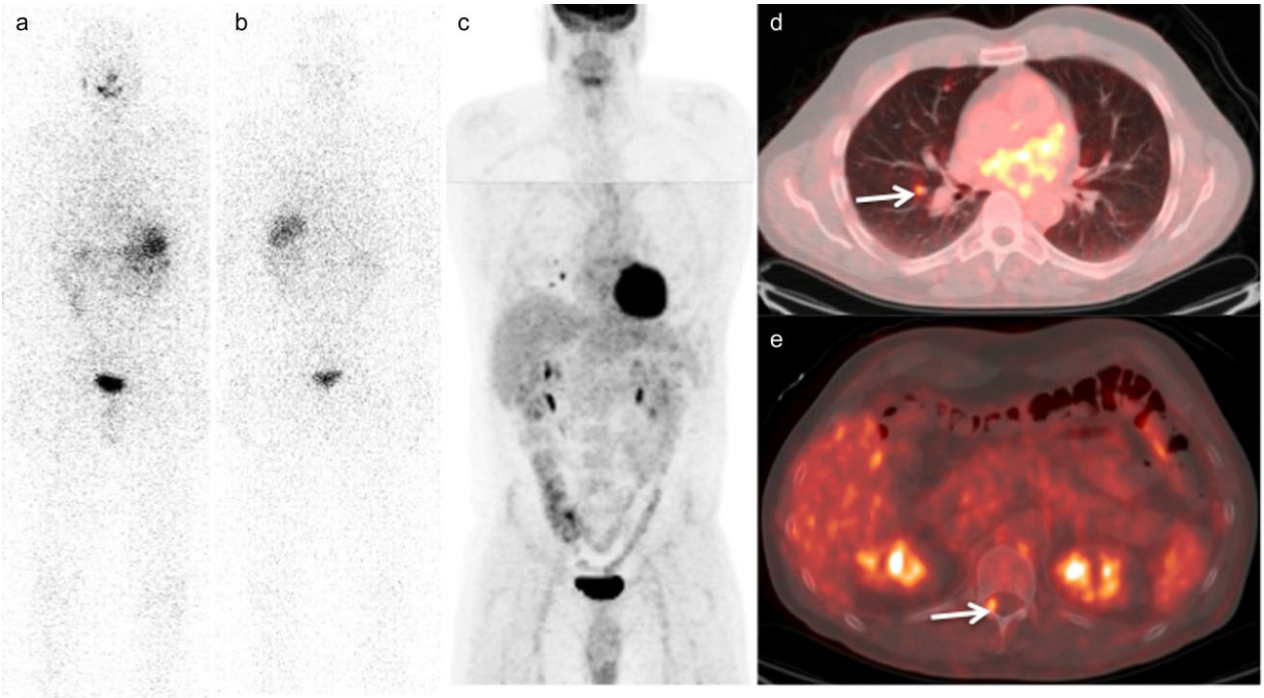

Fig. 1. Positive follow-up PET/CT and outcome: anterior (a) and posterior (b) planar radioiodine scintigraphy, anterior maximum intensity projection(c), axial fused PET/CT (d, e) images of a 50-year-old man with follicular thyroid cancer who underwent follow-up imaging 5 years after completion of treatment with elevated thyroglobulin. The radioiodine scintigraphy images show a negative study, and the PET/CT study demonstrates increase FDG uptake within multiple pulmonary nodules and the lamina of T12 vertebra, consistent with metastatic disease. Despite treatment, the disease progressed resulting in death 3 years after the study.

Table 1. Characteristics of the 202 patients included in the study

Characteristic	*n* (%)
Age (year)†	
<40	64 (31.7)
40–65	104 (51.5)
>65	34 (16.8)
Sex	
Female	125 (61.9)
Male	77 (38.1)
Race	
White	163 (80.7)
Black/other	39 (19.3)
Histology	
Papillary thyroid cancer (PTC)	184 (91.1)
Follicular thyroid cancer (FTC)	18 (8.9)
Stage	
I	68 (33.7)
II	8 (4)
III	36 (17.8)
IV	26 (12.9)
Unknown	64 (31.7)
Treatment‡	
Surgery	200 (99)
Radiation	11 (5.5)
Chemotherapy	0 (0.8)
RAI	194 (96)
PET/CT outcome	
Negative	89 (44.1)
Positive	113 (55.9)
Died	23 (11.4)

†Mean ± SD, 49 ± 16.2 year. ‡Non-cumulative (i.e. patients could have more than one treatment).

Image analysis

Board certified nuclear medicine physicians interpreted all PET/CT images at the time of study for clinical readings. The clinical reports were retrospectively read and categorised into positive, indeterminate and negative studies by a nuclear medicine postdoctoral fellow. Positive studies clearly stated recurrence of primary disease or evidence of FDG-avid metastasis. Indeterminate studies did not confirm nor deny recurrence and their impressions used language such as: 'indeterminate' or 'cannot exclude recurrence'. Negative studies clearly concluded no evidence of recurrence in the impression. The first positive scan for recurrence was used in the analysis of OS, and all subsequent scans were excluded from the study. Follow-up studies were further grouped based on routine surveillance or secondary to clinical suspicion for recurrence or metastases. Last clinical note of the requesting physician and the indication for the study in the clinical report were analysed to establish clinical suspicion, which was clearly stated as a concern for recurrence or metastasis following positive patient symptoms, positive physical exam, rising Tg in the setting of a negative whole body iodine scan, or review of a recent CT scan with suspicious findings. For routine PET/CT scans, the scans were performed as part of routine follow-up without a clear indication of disease or recurrence or metastasis.

Outcome measures

The primary clinical endpoint of the analyses was OS, which was defined as the time between follow-up FDG PET/CT scan and death. For each patient, the date of the PET/CT scan was recorded. Additionally, the date of death was recorded from review of medical records and a public registry of death (http://www.ancestry.com[17]). Patients who were alive were censored at the time of last clinic visit.

Results

Categorisation of PET/CT result

A total of 327 FDG PET/CT scans were obtained from 202 thyroid cancer patients (77 male, 125 female). Of these patients, 93.6% (189/202) had one to three scans and 6.4% (13/202) had four to six scans. For clinical utility purpose, the negative and indeterminate reports were grouped as 'negative for tumor recurrence or metastasis' and positive reports were grouped as 'positive for tumor recurrence or metastasis'. PET/CT scans for recurrence or metastasis were negative in 166 scans and positive in 161 scans. Of the negative scans, 49.4% (82/166) were completed 6–48 months after treatment and 50.6% (84/166) were completed greater than 48 months after primary treatment completion. Of the positive scans, 53.4% (86/161) were completed 6–48 months after primary treatment and 46.6% (75/161) were completed greater than 48 months or more after primary treatment completion.

Cox regression models and patient outcome

Age, gender, race, histology (papillary carcinoma vs. follicular), stage (*early stage* defined as stage I or II vs.

Table 2. Histopathology details of patients with available histopathology reports (n = 99)

Histology	No extrathyroidal or lymphovascular or perineural invasion	Extrathyroidal and/or lymphovascular and/or perineural invasion
	n (%)	*n* (%)
Papillary thyroid cancer		
Conventional type	25 (12.4)	44 (21.8)
Tall cell variant	4 (2.0)	9 (4.5)
Hurthle cell/Oncocytic variant	2 (1.0)	1 (0.5)
Follicular variant	4 (2.0)	6 (3.0)
Foci of anaplastic carcinoma	2 (1.0)	
Follicular thyroid cancer	2 (1.0)	

Table 3. Cox regression analysis

Univariate Cox regression analysis			
	Estimate	95% CI	*P*-value
Age	0.05	0.03, 0.07	<0.0001*
Gender	–0.16	–0.47, 0.14	0.2865
Race	0.45	–0.004, 1.05	0.0521
Histology	–0.42	–0.94, 0.30	0.2171
Stage			<0.0001*
I–II	–1.78	–2.99, –0.98	
III–IV	1.21	0.70, 1.87	
Treatment	–9.0	–17421, 17403	0.5176
RAI	–10.0	–18298, 18278	0.0886
Time to scan	–0.01	–0.01, –0.002	0.0061*
Clinical suspicion	0.25	–0.15, 0.60	0.2069
PET positive	–0.91	–1.33, –0.55	<0.0001*
Multivariate Cox regression analysis			
Age	0.02	–0.001, 0.05	0.0585
Stage			<0.0001*
I–II	–1.77	–3.0, –0.88	
III–IV	1.03	0.47, 1.73	
Time to scan	–0.001	–0.02, –0.61	0.0005*
PET positive	–0.86	–1.40, –0.61	<0.0001*

*Significant variables. χ^2: 86.0 ($P < 0.0001$); Log-likelihood: 43.0. Without PET: χ^2: 54.6 ($P < 0.0001$); Log-likelihood: 27.3.

advanced stage, defined as stages III or IV), treatment type (surgery vs. other), post-surgical RAI treatment and PET/CT result (positive for tumour vs. negative for tumour) were included in the univariate and multivariate Cox regression models. Significant variables in the univariate analysis included age, stage, time-to-scan and PET/CT result. Only variables significant in the univariate analysis were included in the multivariate Cox model. When adjusting for these covariates, stage ($P < 0.0001$), time-to-scan ($P = 0.0005$) and PET/CT result ($P < 0.0001$) were the only variables significantly associated with OS (Table 3). We also performed a hierarchical regression analysis including the statistically significant clinical variables from the univariate analysis in the first step and then included PET/CT result in the second step. There was statistically significant change in the model statistics (Log likelihood 27.3 and chi-square 54.6 to Log likelihood 43.0 and χ^2 86.0; $P < 0.0001$).

PET/CT result and Kaplan–Meier survival analysis

Of the 327 studies included in this study, 161 were positive for recurrence and 166 were negative. A total of 23 patients died during the study period: 21/23 (91.3%) had at least one positive PET/CT scan and 2/23 (8.7%) had all negative PET/CT scans ($P < 0.0001$). Of the 23 patients who died, 20 (87%) had papillary thyroid cancer and three (13%) had follicular histopathology. The Kaplan–Meier analysis based on PET/CT scan results showed a significant difference in OS between those who had a positive PET/CT scan and those who had a negative scan (log-rank, $P < 0.0001$, hazard ratio (HR) (95% CI) = 6.1 (3.0–14.3)) (Fig. 2). A similar subgroup analysis demonstrated a significant difference in OS between PET-positive and PET-negative groups in 168 scans completed between 6–48 months (log-rank, $P < 0.0001$, HR (95% CI) = 7.8 (3.0–26.4)) and in 159 scans completed after 48 months (log-rank, $P = 0.0020$, HR (95% CI) = 3.7 (1.2–13.9)), following primary treatment completion (Fig. 3a,b). The study also demonstrated a significant difference in OS between PET-positive and PET-negative groups among patients with advanced stage disease (III & IV) (log, rank, $P = 0.0001$, HR [95% CI] = 5.6 (2.5–14.4). There was no such significant difference in OS among patients with early stage disease (Fig. 3c,d).

PET/CT results by clinical assessment

We evaluated the added value of FDG PET/CT to clinical assessment in follow-up at the time of the PET/CT scan. Of the 327 scans, 50 (15.3%) were obtained for routine follow-up without clinical suspicion of recurrent disease and 277 (84.7%) were obtained to evaluate for suspected disease. In the context of clinical assessment, PET/CT identified recurrence or metastasis in 50% (25/50) of scans performed without prior clinical suspicion and ruled out recurrence or metastasis in 36.8% (102/277) of scans performed with prior clinical suspicion (Fig. 4, Table 4).

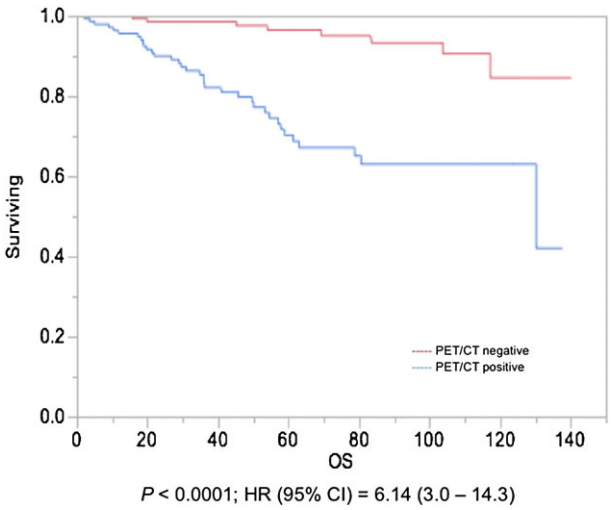

Fig. 2. Kaplan–Meier survival plot for all scans ($n = 327$) in our study. OS between scans with positive and scans with negative PET/CT for thyroid tumour recurrence or metastasis differed significantly.

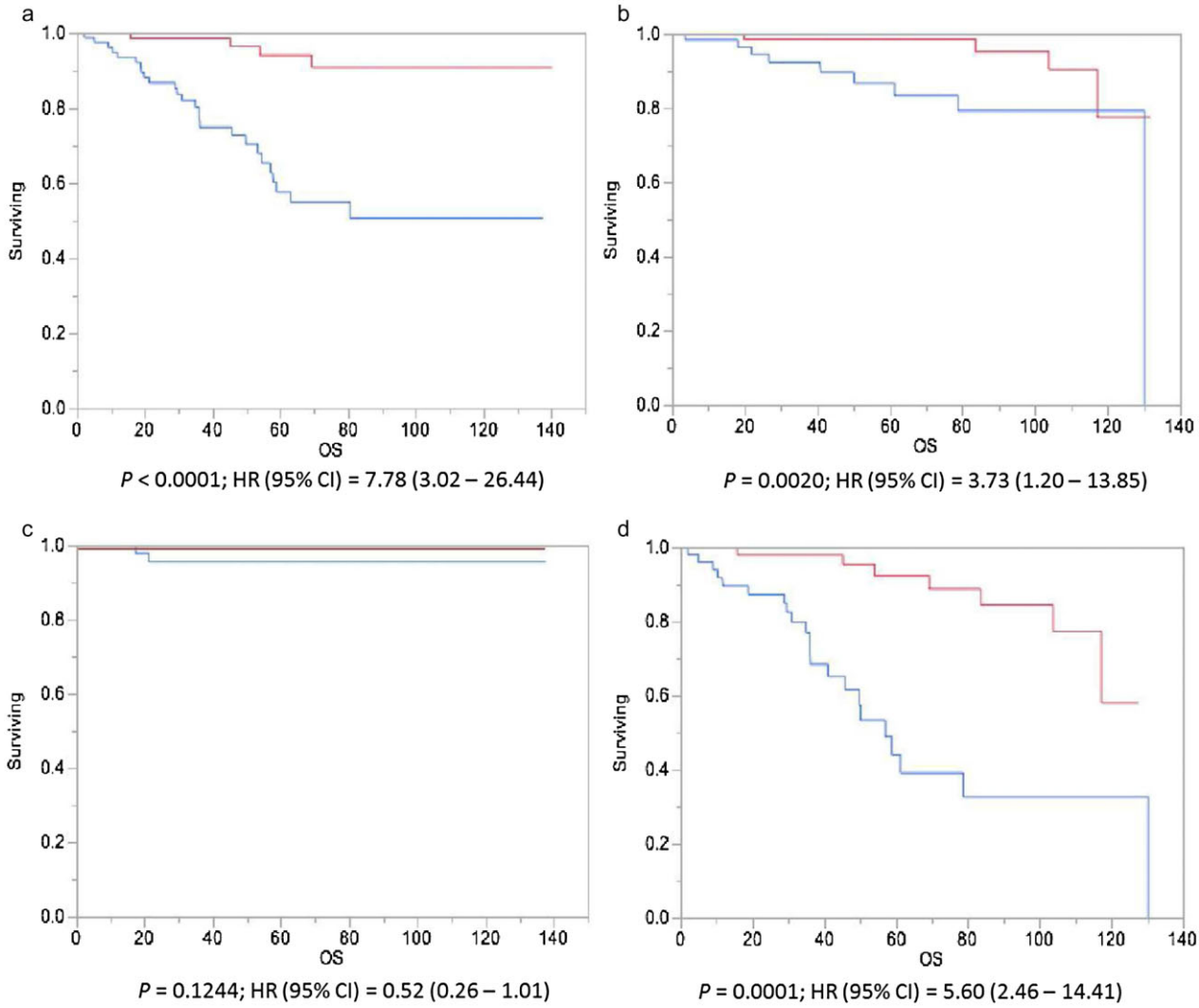

Fig. 3. (a and b) Kaplan–Meier survival plots by time to scan. Overall survival for patients with scans performed 6–48 months after treatment (a) and scans performed more than 48 months after treatment (b). OS differed significantly between positive and negative PET/CT scan results for thyroid tumour recurrence or metastasis scans in patients with scans 6–48 months after treatment and in patients with scans more than 48 months post-treatment completion. (c and d) Kaplan–Meier survival plots by stage: early vs. advanced. Scans were performed in patients with early stage (I & II) (a) or advanced stage (III & IV) (b) thyroid cancer. OS differed significantly between patients with positive and negative PET/CT scan results for thyroid tumour recurrence or metastasis in patients with advanced stage cancer only. No deaths occurred in the early stage patients with a negative PET/CT during the study period.

Discussion

The objective of the study was to evaluate the prognostic value of FDG PET/CT on OS of differentiated thyroid cancer patients following completion of treatment performed in the presence or absence of clinical suspicion prior to the study more than 6 months from the completion of primary treatment. Our study showed that PET/CT is a significant predictor of OS in patients with thyroid cancer performed at any time after treatment completion, especially in patients with advanced stage cancers. In patients with early stage disease, there was no such difference. Additionally, PET/CT identified recurrence or metastasis in 50.0% of scans performed without prior clinical suspicion and ruled out recurrence or metastasis in 36.8% of scans performed with prior clinical suspicion.

In the follow-up of DTC, FDG PET/CT has a distinct role in the follow-up of RAI negative thyroid cancer lesions with an elevated Tg level and has an impact on treatment planning and prognosis.[10,15,16,18] Although there is substantial literature supporting the use of FDG PET/CT scan in patients with elevated Tg levels, there is no clear mention of the optimal timing and frequency of PET/CT

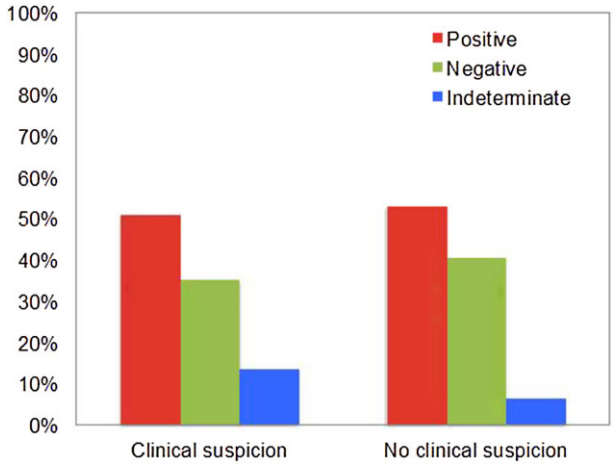

Fig. 4. Added value of PET/CT to clinical assessment. PET/CT was helpful in excluding tumour in 36.8% (102/277) of scans ordered with clinical suspicion of recurrence and identifying recurrence in 50% (25/50) of scans ordered with no prior clinical suspicion.

studies in DTC.[19–21] The ATA recommends a FDG PET/CT to be considered when RAI scan does not identify persistent disease. The indication for a PET/CT study seems to be tailored to the clinical scenario and risk stratification of the individual patient.[22]

In our study, PET/CT detected recurrent or metastatic disease in 50.0% of scans performed without prior clinical suspicion and excluded disease in 36.8% of scans performed with prior clinical suspicion. In current evidence-based clinical practice, a follow-up FDG PET is performed in DTC patients with history of elevated Tg with a negative RAI study with no evidence of recurrent disease, in the follow-up of patients with history of metastatic disease or in patients with invasive Hurthle cell thyroid cancer (HTC).[22] Among the 327 scans, 84.7% of the studies were obtained because of prior clinical suspicion and 15.3% studies were obtained as part of a routine follow-up. Although half of the PET/CT studies performed without prior clinical suspicion were positive, this could be the result of a high-risk group of patients with disease identified earlier in the follow-up period and patients continued to be on surveillance, without symptoms or signs before the follow-up scans. Considering the indications of PET/CT studies in the evaluation of patients with differentiated thyroid cancer, our observation of the indication for the studies is relevant. The number of routine studies demonstrated almost similar proportion with 43.7% studies requested between 6 and 48 months following treatment, and 56.3% studies requested after 48 months. Similarly, among the studies requested with prior clinical suspicion, 51.1% studies were requested between 6 and 48 months after treatment completion, and 48.8% studies were requested after 48 months of completion of treatment. These observations show that a PET/CT study performed with prior clinical suspicion is more likely to be positive.

In patients with DTC, established common prognostic factors are distant metastasis, incomplete surgical resection, tumour stage, vascular invasion, Hurthle cell histology and male gender.[23–27] Robbins *et al*.[28] evaluated the prognosis for metastatic thyroid carcinoma in 400 thyroid cancer patients and found that age and PET result were strong predictors of survival in the multivariate analysis. In the multivariate Cox regression analysis in our study, we have observed that only stage, time-to-scan and the PET result were significantly associated with OS. Although tumour stage and PET results have been demonstrated as significant factors in the above-mentioned studies, time-to-scan has not been specifically evaluated as a significant factor in these. This can be related to more aggressive disease leading to an early PET scan in follow-up and detection of recurrence. Inclusion of PET/CT result to the hierarchical regression analysis in the second step to other significant covariates revealed significant change in the survival prediction model. This observation shows that the added effect of PET/CT result for survival after all other significant clinical covariates considered in the survival prediction model.

We acknowledge limitations to the current study. This a retrospective study and the errors of confounding are not controlled as for prospective studies. The results of the PET/CT studies were ascertained from the review of the clinical reports, but the images were not reviewed. The PET results included indeterminate results, the cause of which we have not analysed. The cancer stage was not reported in the electronic medical records of all patients, and the effect of clinical stage on OS could have been underestimated. We did not ascertain the histology

Table 4. Clinical suspicion PET/CT results

PET/CT result	Routine *n* (%)	Clinical suspicion *n* (%)	Total *n* (%)	*P*-value
Positive	25 (7.7)	136 (41.6)	161 (49.2)	$P = 0.4726$*
Negative	21 (6.4)	102 (31.2)	123 (37.6)	
Indeterminate	4 (1.2)	39 (11.9)	43 (13.2)	
Total	50 (15.3)	277 (84.7)	327 (100)	

*Pearson χ^2 test.

of potential recurrences. Certain factors such as Tg doubling time[29] could not be included in the analyses because of the time interval between the studies and the tests in some patients.

Conclusion

FDG PET/CT performed in the follow-up more than 6 months from primary treatment completion is a prognostic marker of OS in thyroid cancer patients, performed at any time after treatment completion, especially in patients with advanced stage disease (stages III and IV). PET/CT also adds value to clinical assessment by excluding recurrence or metastasis in 36.8% of patients suspected of disease and identifies recurrence in 50% without prior clinical suspicion.

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