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ORIGINAL ARTICLE

Comparison of F-18 FDG-PET/CT and Tc-99m MIBI in the preoperative evaluation of cold thyroid nodules in the same patient group

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Abstract Recent studies have reported that standardized uptake values of FDG-PET imaging might predict malignant thyroid nodules and can be used in the preoperative evaluation of thyroid lesions. The aim of our study was to evaluate FDG-PET imaging in patients with cold thyroid nodules and to compare the imaging findings with Tc-99m MIBI scans and with post-op histopathology results. Twenty-three patients (18F, 5M) with 24 nodules that were suspicious in ultrasound and cold in Tc-99m pertechnetate scan, were included in the study. Each nodule underwent sonographically guided fine-needle aspiration biopsy. FDG-PET and MIBI scans were performed with an interval of 3–5 days. All patients underwent thyroidectomy and their FDG-PET, and MIBI thyroid scan results were compared with post-thyroidectomy pathology results. Post-op histopathology results found 7 malignant and 17 benign nodules. Six of the seven malignant nodules had increased uptake, which were positive for malignancy in both PET and MIBI scans. Each imaging method used different radiopharmaceuticals but showed one false-negative result in two different patients. FDG-PET produced false positives in eight nodules and MIBI scans found false positives in four nodules. FDG-PET imaging and MIBI scan showed the same sensitivity in malignant nodule evaluation, but their specificity differed. As a result, we suggest that FDG-PET imaging is not superior to MIBI scanning in differentiating malignant from benign thyroid nodules. MIBI imaging should be the first choice in the preoperative evaluation of patients with cold thyroid nodules as an adjunct procedure to FNAB because of its low cost and availability. This imaging technique can be used routinely in patients who are reluctant to undergo FNAB.

Keywords Thyroid nodule · Scintigraphy · MIBI · FDG-PET/CT

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Introduction

Thyroid nodules are common and exist in up to 50 % of the adult population [1]. Most thyroid nodules are benign hyperplastic lesions, but 5–20 % of thyroid nodules are true neoplasms and the incidence of thyroid malignancy in the general population is 40–1000 cases per million per year [2, 3]. One of the major goals in the evaluation of solitary thyroid nodules is the differentiation of hyperplasia from true neoplasms. In thyroid cancers, initial diagnosis, and early identification are important for the selection of the appropriate treatment, delays in diagnosis are associated with increased mortality [4, 5].

The initial evaluation of a thyroid nodule includes measurement of serum thyroid-stimulating hormone (TSH), ultrasonography (US), Tc-99m pertechnetate scintigraphy, and fine-needle aspiration biopsy (FNAB). FNAB has become the most important tool in the assessment of solitary thyroid nodules [6]. However, a number of reports have shown that between 10 and 30 % of FNAs of thyroid lesions are reported as indeterminate [7].

Techniques that have been used to characterize whether thyroid nodules are benign or malignant include conventional ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), color doppler sonography, conventional scintigraphy with radioactive iodine or technetium 99m, Thallium-201, and Tc-99m methoxy-isobutyl-isonitrile (MIBI) scintigraphy [8]. MIBI scintigraphy in combination with FNAB has been used for many years, in the diagnosis of scintigraphically cold and therefore suspicious thyroid nodules [9]. Nowadays, FDG-PET/CT is commonly used in clinical practice, which has led to an increase in the detection of incidentalomas. Previous studies have shown a correlation between a positive FDG-PET and the presence of thyroid carcinoma within thyroid incidentalomas and multi-nodular goiters [10, 11].

The aim of our study was to compare FDG-PET and Tc-99m MIBI scintigraphy with both FNAB and post-op histopathology results in cold thyroid nodules.

Materials and methods

This study was approved by the institutional ethical committee. Twenty-three patients with 24 nodules that were suspicious for malignancy in ultrasound and cold in Tc-99m pertechnetate scan were included in the study. For this study, the inclusion criteria were (1) normal TSH level (reference range, 0.4–4.0 ng/mL); (2) suspicious ultrasound examination; (3) nodules more than 10 mm diameter; and (4) hypofunctioning in a Tc-99m pertechnetate scan. Patients were excluded from the study if they were pregnant, breast-feeding, or unable to undergo surgery.

All patients gave informed consent and each underwent FNAB, early–late Tc-99m MIBI scintigraphy, whole-body FDG-PET/CT, and thyroidectomy.

During the thyroid ultrasound examination, which was performed by an experienced physician, any solitary thyroid nodule was considered suspicious if it was larger than 10 mm with irregular margins, had chaotic intranodular vascular spots, was rounded or with a taller-than-wide shape, or had microcalcifications. Routine thyroid scintigraphy was performed 15 min after an intravenous injection of 74–185 MBq of Tc-99m pertechnetate to rule out patients with hyperfunctioning (*or hot*) nodules. FNAB procedures were performed under US with the patients' neck hyperextended. The needle (22–25 G) was inserted obliquely within the transducer plane of view and contents of needles were expelled onto glass slides and smeared with a second slide to spread fluid across the surface. All samples were evaluated by the same experienced cytopathologist, who was blinded to the clinical and imaging findings. All biopsies were attempted only once so as not to affect features of the imaging procedures, such as inflammatory response.

FDG-PET/CT and MIBI scintigraphy were performed with an interval of 3–5 days. Tc-99m MIBI scans were obtained 30 and 120 min after IV administration of 370 MBq of Tc-99m MIBI (Cardiolite, Bristol–Meyers–Squibb, North Billerica, MA). All scans were obtained in the anterior projection of the neck using a gamma camera (Mediso, Nucline Spirit DH-V, Hungary) equipped with a high resolution, parallel-hole, low-energy collimator. Images were obtained in a 128 $\times$ 128 matrix using a digital zoom of 2. The acquisition time was set to 600 s with a 20 % window centered at 140 keV in all cases. Tc-99m MIBI images were evaluated visually and semi-quantitatively. MIBI scans were reported as negative if the thyroid nodule showed no MIBI uptake, and positive if the nodule showed MIBI uptake. Tumor/normal thyroid gland (T/N) uptake in the early and late MIBI images was quantitatively assessed. Regions of interest (ROIs) were drawn on the images. Both images were then displayed together and manually observed ROIs were drawn on the nodule, the contralateral thyroid tissue, and the surrounding extrathyroidal tissue. Nodule/background MIBI uptake (as ROI count) on the early and late images was calculated; if the late nodule/background calculation was higher than one, it was accepted as a positive MIBI image result. This kind of visually and semi-quantitatively analysis has been described in other studies [12, 13]. Washout rate can be calculated from early and late tumor/normal background activity.

A whole-body F-18 FDG-PET/CT imaging was performed with a 6-slice multi-detector CT-integrated high resolution PET scan (Siemens, Biograph LSO HI-REZ PET/CT, Illinois, USA). All patients fasted 4–6 h prior to the F-18 FDG tracer administration. Sixty minutes of uptake time was allowed after the intravenous injection of 370–555 MBq (10–15 mCi) of F-18 FDG, during which the patient was asked not to talk, chew gum or perform other repetitive activities, a whole-body scan was performed. In the FDG-PET imaging, SUVmax ratio is being used for quantitative analysis and if SUVmax ratio is higher than 2.5, any lesion in mediastinum and lung is accepted as positive [14]. On PET/CT scans, focal or diffuse thyroid gland FDG uptake can be seen in the nodule area [15]. In the present study, focal or diffuse uptake within the thyroid gland in the nodule area with a maximum standard uptake value (SUVmax) of greater than background in the FDG-PET scan was considered to be a positive lesion.

Total thyroidectomy was performed in all patients and a final histologic diagnosis was obtained after examination of the permanent sections of the surgical specimens. Each FDG-PET/CT scan was reviewed by the nuclear medicine physician and all FNAB cytopathologic-surgical histopathologic evaluations were evaluated by the thyroid pathologist.

Results

Patient characteristics, post-op histopathology, SUVmax values, T/N uptake ratio from early–late MIBI, and sizes of the 24 nodules are summarized in Table 1. The average patient age was 49.1 ± 10.6 years (range 29–72 years). Seventy-eight percent (18/23) of the patients were women.

All needle biopsies were attempted only once time so as not to affect features of the imaging, such as false positive inflammatory responses. Fine-needle aspiration biopsy results were malignant for 4 nodules (16.6 %) (Bethesda DC VI), benign for 10 nodules (41.6 %) (DC II), and revealed non-diagnostic (DC I) or DC III = atypia/follicular lesions of undetermined significance (AUS/FLUS) in 10 nodules (41.6 %). Sensitivity, specificity, PPV, and NPV for FNAB were calculated as 57.1, 100, 100, 76.9 %, respectively. Post-op histopathology revealed 7 malignant (29.1 %) and 17 benign (70.8 %) nodules (14 adenomatous nodules, 2 adenomas, and 1 lymphocytic thyroiditis). Of the 7 malignant nodules, 6 were positive for malignancy in both the PET and MIBI scans. We were unable to differentiate adenomas from malignant nodules that were positive for malignancy in both imaging modalities. Each radiopharmaceutical showed 1 false-negative result in two different patients (Patient number 10 for FDG-PET imaging and patient number 7 for MIBI imaging). There were 8 false-positive nodules with FDG-PET (33.3 %) and 4 with MIBI (16.6 %). The accuracy, specificity, positive predictive value of FDG-PET was calculated as 62.5, 52.9, and 42.8 %, respectively. The negative predictive value of FDG-PET was calculated as 90.0 %. FDG-PET and MIBI showed the same sensitivity but different specificity in detecting malignant nodules. The accuracy, specificity, positive predictive value of MIBI was calculated as 79.1, 76.4, 60.0 %, respectively. The negative predictive value of MIBI was calculated as 92.8 %.

Discussion

It has been the goal of nuclear medicine physicians and radiopharmacists to find a radiopharmaceutical with specific uptake in malignant thyroid nodules and Tl-201, Ga-67, Tc-99m MIBI, and Tc-99m Tetrofosmin have been used for this purpose [16]. Differentiation of malignant and

Table 1 Post-op histopathology, SUVmax values, T/N uptake ratio early and late MIBI images of 23 Patient

P	Sex	Age	Post-op HP	SUVmax values	T/N UR (early/late)	Nodul size (cm)
1	F	43	A H	1.4 (TN)	0.7–0.8 (TN)	3.5
2a	F	36	Follicular Ca	7.1 (TP)	2.7–3.1 (TP)	2.5
2b	F	36	AH	1.2 (TN)	0.8–0.7 (TN)	1.7
3	M	54	AH	2.1 (TN)	1.6–1.4 (FP)	1.5
4	M	56	AH	3.5 (FP)	1.3–1.0 (TN)	4.1
5	F	44	Follicular adenoma	2.8 (FP)	1.2–1.3 (FP)	2.6
6	F	29	Lym. Thyroiditis	10.5 (FP)	2.1–1.6 (TN)	3.3
7	F	38	Papillary Ca	3.5 (TP)	1.3–1.0 (FN)	3.8
8	M	61	AH	3.5 (TP)	1.2–1.0 (TN)	1.3
9	F	66	Papillary Ca	4.0 (TP)	3.1–2.2 (TP)	4.0
10	F	39	Papillary Ca	1.5 (FN)	1.7–1.3 (TP)	1.5
11	F	55	AH	2.1 (TN)	1.3–1.2 (FP)	3.3
12	M	51	AH	3.1 (FP)	1.4–0.9 (TN)	4.6
13	F	42	AH	2.4 (TN)	1.6–1.0 (TN)	5.4
14	F	72	Papillary Ca	3.1 (TP)	1.5–1.4 (TP)	1.9
15	F	38	AH	3.7 (FP)	1.5–0.9 (TN)	4.2
16	F	48	AH	2.0 (TN)	1.0–1.0 (TN)	2.6
17	M	52	AH	1.2 (TN)	1.1–1.0 (TN)	4.4
18	F	49	AH	0.8 (TN)	1.3–1.0 (TN)	2.2
19	F	57	Papillary Ca	16 (TP)	1.3–1.5 (TP)	3.0
20	F	48	Hurthle Ca	9.9 (TP)	2.1–1.9 (TP)	4.2
21	F	63	AH	3.8 (FP)	2.2–0.8 (TN)	2.8
22	F	57	AH	1.8 (TN)	2.2–0.8 (TN)	1.9
23	F	46	Follicular adenoma	6.2 (FP)	1.8–2.1 (FP)	4.5

P patient, *AH* adenomatous hyperplasia, *TP* true positive, *TN* true negative, *FP* false positive, *FN* false negative, *T/N UR* tumor/normal thyroid gland uptake ratio, *HP* histopathology benign thyroid tissue is difficult because adenomas always have a different scintigraphic appearance to adenomatous nodules.

An adenoma is histopathologically defined as a solitary encapsulated tumor with a uniform internal architecture that is substantially different from the surrounding thyroid parenchyma and compresses the adjacent gland. An adenomatoid nodule is typically one of many nodules, poorly encapsulated, with a varied architecture that resembles the surrounding gland more closely, and does not compress the adjacent tissue. Solitary nodules that appear histologically identical to the multiple nodules seen in nodular goiter are also called adenomatoid nodules [17]. Some studies have reported that adenomas tend to accumulate high amounts of radiotracer and show slow clearance (Tc-99m MIBI and Tc-99m Tetrofosmin), which makes it difficult to differentiate them from malignant thyroid tumors [18, 19]. Figure 1 shows F-18 FDG-PET and Tc-99m MIBI images of a patient with an adenomatous nodule (Fig. 1a, b).

FNAB is the most important tool in the assessment of solitary thyroid nodules in differentiating between benign and malignant solid thyroid nodules. However, a number of reports have shown that FNABs of thyroid lesions are reported as indeterminate and repeat biopsies are required. Some patients with solitary thyroid nodules whose FNAB is indeterminate may undergo surgery; consequently, there is need to identify patients who are likely to have thyroid carcinoma and need surgery [20]. Our study was designed to compare FDG-PET/CT and early/late Tc-99m MIBI with both FNAB and post-op pathology results in cold thyroid nodules.

In recent years, F-18 FDG-PET has been shown to effectively detect various types of cancers by virtue of their increased glucose metabolism [21]. Several studies have also used F-18 FDG to detect malignant thyroid tumors. F-18 FDG-PET/CT has been demonstrated to show metastasis in patients with I-131 scan-negative thyroglobulin (tg) positive thyroid cancer with a high accuracy

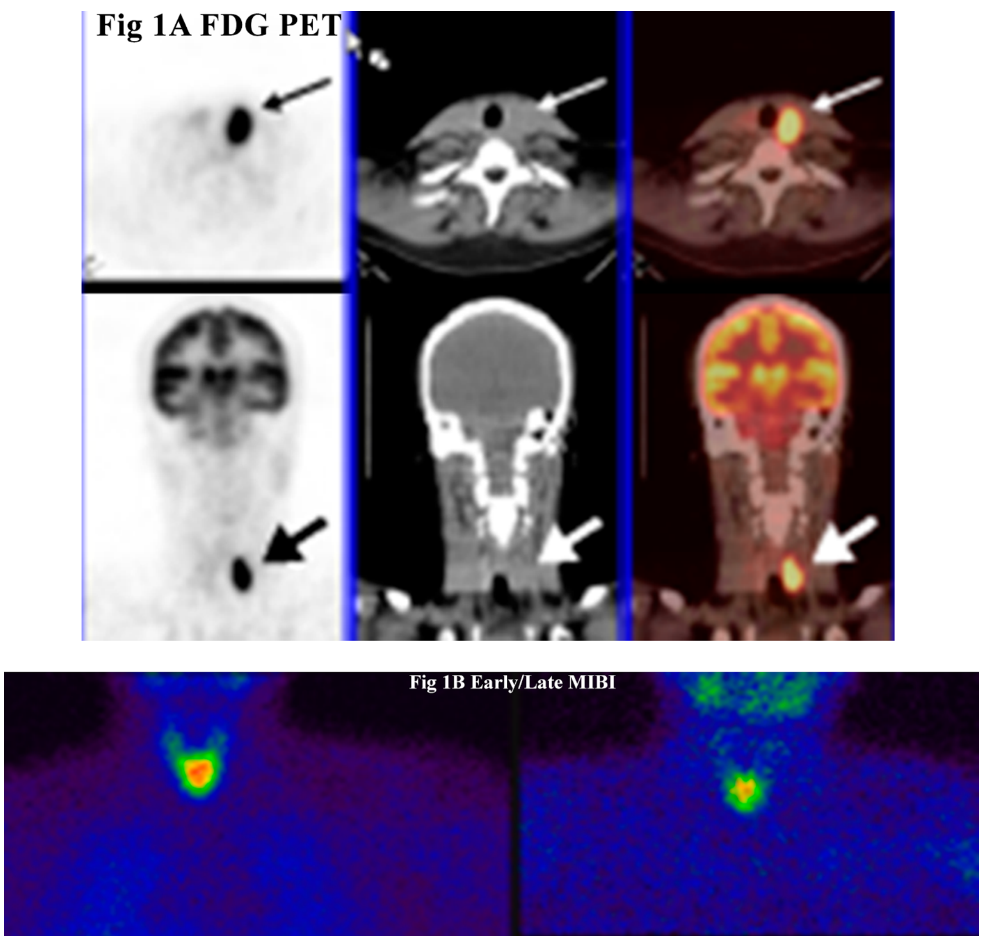


Fig. 1 **a**, **b** F-18 FDG-PET/CT images show slightly increased FDG uptake with a 2.1 SUVmax value. Early–late phase of Tc-99m MIBI images show focal increased activity in a nodule of the right thyroid gland. Early T/N uptake value is 1.6 and late T/N uptake value is 1.4. Histopathological diagnosis of this nodule was adenomatous nodule (Patient no. 3)

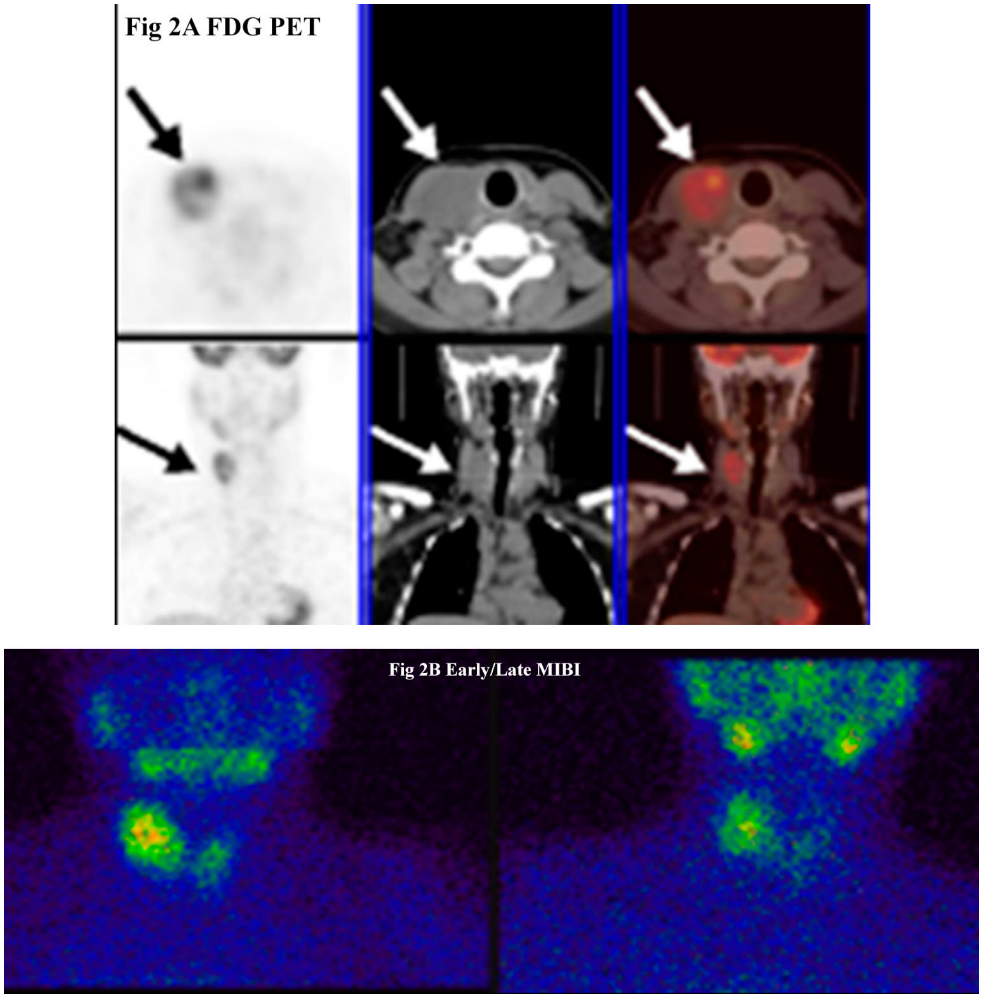


Fig. 2 **a**, **b** F-18 FDG-PET/CT image shows increased FDG uptake with a 6.2 SUVmax value and early–late phase of Tc-99m MIBI scan show focal increased activity in a nodule of the right thyroid lobe. Early T/N uptake value is 1.8 and late T/N uptake value is 2.1. Histopathological diagnosis of this nodule was follicular adenoma (Patient no. 23)

[22]. Incidentalomas are non-palpable nodules detected under US or other anatomic imaging techniques. FDG-PET is commonly used in clinical practice, which has led to an increase in the detection of incidentalomas. Previous studies have documented that the risk of malignancy has a wide range between 10 and 63.6 % in incidentalomas, which may be due to variability in population characteristics and the background risk of thyroid disease relative to the geographic area [23]. However, PET/CT does not provide additional information to that yielded by US for routine nodule evaluation and for the preoperative assessment of thyroid cancer, and is associated with greater expense and radiation burden. Incidental thyroid nodules that are seen as positive in PET/CT imaging should be carefully examined and FNAB should be performed.

Researchers had expected that increased the FDG uptake in malignant thyroid nodules would enable the differentiation between benign and malignant thyroid nodules; however, the high SUVmax values of adenomas, which are similar to malignant nodules, especially Hurthle cell adenomas, have also been problematic in FDG studies [24]. In our study, two patients had follicular adenomas (patient 5 and patient 23) that FDG-PET and MIBI images showed as malignant (Figs. 2a, b), thus we were unable to differentiate follicular adenomas from malignant nodules, which is consistent with findings in the literature. Giovanella et al. reported that four F-18 FDG positive benign lesions in their series were follicular adenomas and concluded that follicular lesions require definitive histological confirmation because neither US cytology nor frozen section were able to discriminate benign follicular adenoma from malignant thyroid carcinoma [25]. On the other hand, one of the nodules in our study that had positive uptake and indicated malignancy in both the FDG-PET and MIBI images, was revealed to be follicular carcinoma in the post-op pathology results (Fig. 3a, b).

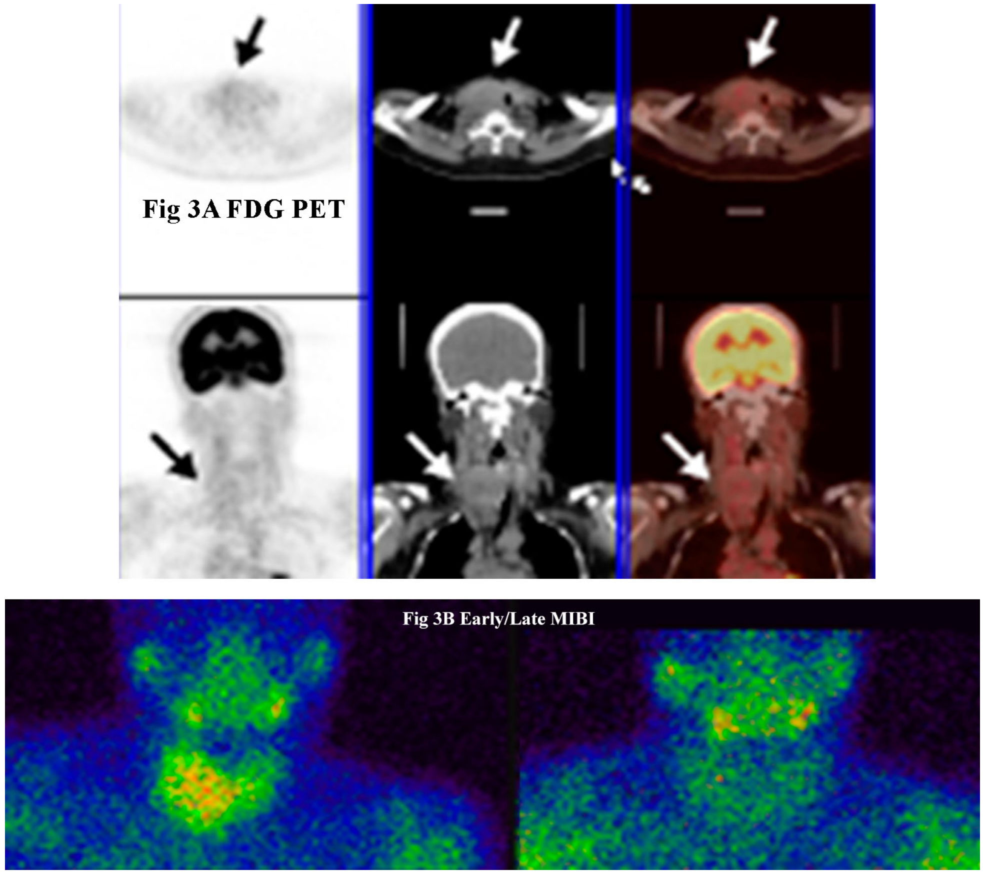


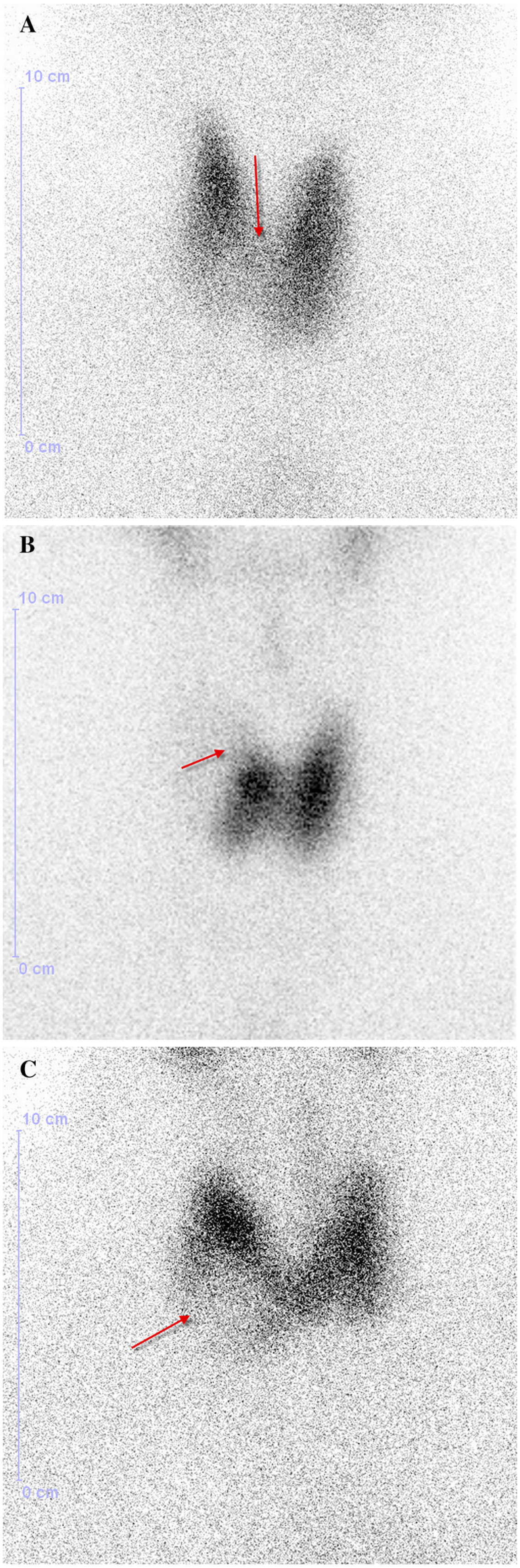
Fig. 3 **a**, **b** F-18 FDG-PET/CT CT image shows focal increased FDG uptake with a 16 SUVmax value and early–late phase of Tc-99m MIBI scan show focal increased activity in a nodule of the left thyroid lobe. Early T/N uptake value is 1.3 and late T/N uptake value is 1.5. Histopathological diagnosis of this nodule was papillary thyroid carcinoma (Patient no. 19)

The Tc-99m MIBI has been reported to accumulate in differentiated thyroid carcinomas and medullary thyroid carcinomas in recurrence or metastatic lesions [26]. FDG-PET and MIBI can also be used for cancer diagnosis in medullary thyroid cancers; however, we had no patients with medullary thyroid cancer in this group. Several groups have tried to identify differences between benign and malignant hypofunctioning solid thyroid nodules using MIBI scans. Malignancy was considered when MIBI uptake was more than the in surrounding thyroid tissue. The probability of thyroid malignancy increases in cold and MIBI-positive thyroid nodules, whereas nodules with absent MIBI uptake have been generally proved to be benign [27] (Fig. 4).

The oldest publication of the use of MIBI in the further clarification of suspicious thyroid nodules was performed by Foldes et al., and they concluded that increased, normal, or decreased 99mTc-MIBI accumulation was not specific for thyroid malignancy and that the 99mTc-MIBI uptake depends mainly on the viability of thyroid tissue [28]. Wale et al. showed in their study that compared MIBI scintigraphy with FNAB, MIBI scintigraphy could achieve a very high negative predictive value ranging from 88 to 100 %, with a mean of 97 % [29]. Wale et al. also showed that the addition of MIBI scintigraphy lead to a considerable saving in costs per patient and per cancer diagnosed, while not significantly affecting life expectancy [29]. In the literature, many studies have indicated that there was an increased cancer risk in thyroid nodules with 99mTc-MIBI uptake and a marked decrease in such risk in nodules without 99mTc-MIBI uptake. Reports have also shown the need for surgical removal of nodules with high 99mTc-MIBI uptake [30, 31]. However, some authors have acknowledged that false-negative MIBI scintigraphy findings do occur in thyroid cancer. De Geus-Oei et al. concluded that F-18 FDG accumulation in PET was less than MIBI in benign thyroid nodules and recommended F-18 FDG-PET for patients whose FNAB results were inconclusive and require surgical intervention [32].

One of the limitations of our study is that the patient sample group is small. This study could have been undertaken with a larger patient group. The other limitation concerns nodule size. As mentioned in the introduction, the inclusion criteria required nodules to be sized 1 cm or larger, this was because of the resolution limitation of routine pertechnetate and MIBI scintigraphy.

It should be known that if the MIBI or FDG-PET imaging is done just after the FNAB, this may cause



◀**Fig. 4** **a**, **b**, **c** Corresponding Tc-99m pertechnetate images of patient 3, patient 23, and patient 19 show hypoactive thyroid nodules

inflammatory response. We have waited at least 7 days for the imaging. Also inflammatory response can be seen as linear activity in MIBI or in FDG-PET.

Conclusion

As a result, we suggest that FDG-PET is not superior to MIBI in differentiating malignant nodules from benign nodules; each imaging modality produces false-negative results. MIBI should be the preferred imaging modality in the preoperative investigation of patients for surgical intervention because of its lower cost and availability of MIBI compared with PET/CT. Moreover, Tc-99m MIBI is an adjunct procedure to FNAB and this imaging technique can be used routinely in patients who are reluctant to undergo FNAB.

Conflict of interest There is no conflict of interest.

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