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ORIGINAL SCIENTIFIC REPORT

Risk of Malignancy in FDG-Avid Thyroid Incidentalomas on PET/CT: A Prospective Study

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Abstract

Background Due to a substantial risk of malignancy, patients with focal FDG-avid thyroid incidentalomas (FFTIs) on PET/CT are in most of Denmark referred to Head and Neck Cancer (HNC) fast track programs. The aim of this study was to determine the risk of malignancy in FFTI managed in a HNC fast track program.

Methods A prospective cohort study including all patients with FFTI referred to the HNC fast track program, Odense University Hospital between September 1, 2016 and August 31, 2017. Ultrasonography (US) and fine-needle aspiration biopsy (FNAB) were intended to be done in all patients. Nodules with cytology of Bethesda 1, 3, 4, 5, or 6 were planned for surgical removal.

Results A total of 104 patients were included. All patients had US and 101 patients (97%) had FNAB. Forty-two patients had benign cytology classified as Bethesda 2. The remaining 62 patients underwent surgery except from 11 patients, mainly due to comorbidity. The overall risk of malignancy for patients with FFTI referred to our HNC fast track program was calculated to be 24% (23/95) based on patients with unequivocal cytology and/or histology. The only statistically significant US characteristic to predict malignancy was the appearance of irregular margins with a sensitivity of 47% and specificity of 96%.

Conclusion The risk of malignancy of FFTIs handled in our HNC fast track program is 24%.

Introduction

^{18}F-Fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) is increasingly being used as an imaging modality in the daily clinical routine [1]. This has led to a rising number of focal FDG-avid thyroid incidentalomas (FFTIs) on PET/CT ranging from 0.1 to 4.3% in prevalence [2–4]. A FFTI is defined as an unexpected finding on a PET/CT scan with an area of abnormally increased FDG uptake in the thyroid gland, when the scan is done for a non-thyroid purpose. An increased thyroid FDG uptake may be focal or diffuse, of which the latter is considered as a benign lesion caused by thyroiditis or hypothyroidism [5]. Recent studies have shown that FFTI is associated with a significant risk of malignancy somewhere between eight and 66% [2, 6–15].

The increased use of PET/CT scans combined with the known risk of malignancy which differs considerably among studies, calls for guidelines on how to manage FFTIs. Normally, the risk of malignancy in FFTI is evaluated using ultrasonography (US) often combined with a fine-needle aspiration biopsy (FNAB). This strategy is based on the common belief that non-palpable nodules have the same risk of malignancy as do sonographically

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confirmed palpable nodules of the same size [16]. In accordance with the American Thyroid Association Guidelines from 2015, the sonographically suspicious nodules with a size >10 mm are further evaluated with FNAB [17]. Management is based on both the US and the cytology given by the Bethesda system [18].

During the last decade, multiple studies have addressed the dilemma handling FFTIs [2, 6–15]; and no clinical consensus has been achieved. Most of the studies are designed retrospectively and are limited by selection bias.

In this prospective cohort study, we present a consecutive series of patients referred to the Head and Neck Cancer (HNC) fast track program, Odense University Hospital with FFTI. The aim of this study was to determine the risk of malignancy in FFTIs managed in a HNC fast track program.

Methods

All patients referred to the department of ORL Head & Neck Surgery and Audiology, Odense University Hospital between the September 1, 2016 and August 31, 2017 with FFTI were prospectively included through the HNC fast track program [19]. The inclusion criterium was a focal or multi-focal thyroid FDG uptake in patients without prior history of neoplastic thyroid disease.

Further clinical examination included US of the neck and US-guided FNAB of the FDG-avid nodule. The US of the neck were all performed by experienced head and neck cancer specialists. In addition, also a systematic scan of the lateral neck was performed. The following parameters of the FFTI were noted: echogenicity, largest diameter, presence of micro-calcifications, and irregular margins. Lymph nodes were marked as suspicious by the specialists based on traditional characteristics of malignant lymph nodes, including features as spherical form, irregular architecture, isoechoic density, and micro-calcifications.

Three parallel FNABs were obtained from the FFTI, and the dried slides were sent for analysis to the local department of pathology. The results were reported according to the Bethesda system:

- Bethesda 1: Non-diagnostic/unsatisfactory
- Bethesda 2: Benign lesions
- Bethesda 3, 4, 5, and 6: Atypia, follicular neoplasm, suspicious for malignancy, and malignant

Histological reports for the patients undergoing thyroidectomy were classified as benign or malignant by the pathologist.

Statistics

Mean values are given with confidence interval (95% CI). Comparison between benign and malignant lesions (based on conclusive cytology and histology) was made using Student's unpaired t test and Fisher's exact test. Results were considered statistically significant when $p < 0.05$. All statistical analyses were performed using Stata 15.0 (StataCorp College Station, TX).

Results

A total of 104 patients with FFTI were included. The complete list of indications for the PET/CT scans and patient characteristics are presented in Table 1.

All patients had US done. The average size of the lesions on US was 18 mm (95% CI 16–20 mm) ranging from 5 to 70 mm. There was no difference in the size of malignant and benign FFTI (18 mm (95% CI 12–25 mm) vs. 18 mm (95% CI 16–21 mm), $p = 0.95$). Eleven of the lesions (11%) were smaller than 10 mm in greatest dimension, of which three were with malignant histology (27%), three with benign histology (27%), three with benign cytology (27%), and two (18%) with non-diagnostic cytology who were not operated for reasons stated below.

The highest sensitivity and specificity were given by the appearance of irregular margins. The presence of suspicious lymph nodes was the least sensitive predictor of malignancy. The positive predictive value (PPV), negative predictive value (NPV), sensitivity and specificity, and

Table 1 Patient characteristics and PET/CT data

Patient characteristics	
Age (median (range))	67 (34–90)
Sex (male/female)	33/71
Indication for PET/CT scan (n)	
Suspicion of malignant disease	38
Follow-up on known malignant disease	33
Suspicion of benign disease	30
Follow-up on known benign disease	3
Primary sites of malignancy suspicion (n)	
Other cancers	20
Gynecologic cancer	15
Hematologic cancer	14
Lung cancer	10
Unknown	6
Breast cancer	3
Head and neck cancer	2
Prostate cancer	1

Table 2 Diagnostic values of ultrasound characteristics

Characteristics	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)	*p* values
Micro-calcifications	25	75	26	73	1.0
Irregular margins	78	85	47	96	*<0.005*
Suspicious echo density	32	79	44	69	0.4
Suspicious lymph nodes	33	74	5	97	1.0

p values were calculated for the individual US characteristics and are shown in Table 2.

Further examination with US-guided FNAB was performed in all except of three patients (3%) for different reasons. In two cases, the nodule was inaccessible for practical reasons, and in one case, the nodule was suspected of being a metastasis from a renal clear cell adenocarcinoma. These patients all underwent surgery based on the clinical manifestation. Two patients (67%) had benign histological diagnosis, whereas 1 patient (33%) had histologically verified renal clear cell adenocarcinoma metastasis (see Fig. 1).

Forty-two patients (40%) were already classified as benign based on the FNAB (Bethesda 2) and were only followed up in case of malignant characteristics on US.

Thirty patients (29%) had cytology categorized as Bethesda 3, 4, 5, or 6. After surgical intervention, 15 of these (50%) ended up with a benign histological diagnosis, while 11 (37%) had cancer. Four patients (13%) were not operated.

Twenty-nine patients had Bethesda 1 cytology (28%). Histology showed benign lesions in 13 of these patients (45%), whereas malignancy was diagnosed in 9 of the cases (31%). Seven patients (24%) were not operated.

In total, 11 patients did not undergo surgery due to either comorbidity ($n = 5$), patients' decision ($n = 3$), nodule less than 10 mm on US ($n = 2$), or biochemistry consistent with Hashimoto's thyroiditis ($n = 1$). On FNAB, two of these patients had cytology with Bethesda 6 showing metastatic cells from lung cancer or sarcoma. They were not operated since their primary cancer disease did not allow so. The remaining nine patients that did not undergo surgery were either Bethesda 1 ($n = 7$) or 4 ($n = 2$).

Thus, 24% (23 patients of 95 with histology or conclusive cytology) had histologically or cytologically verified thyroid cancer, where most of them were papillary carcinomas ($n = 17$). All malignant cases are presented in Table 3.

Discussion

Incidental findings of thyroid nodules are very common using US and CT, with a prevalence up to 50% in patients older than 50 years [20]. However, the risk of malignancy is relatively low (5%) and is independent of nodule size as the risk of malignancy is similar in the incidentaloma compared to the palpable thyroid nodule [21]. An accurate determination of the risk of malignancy is still lacking in

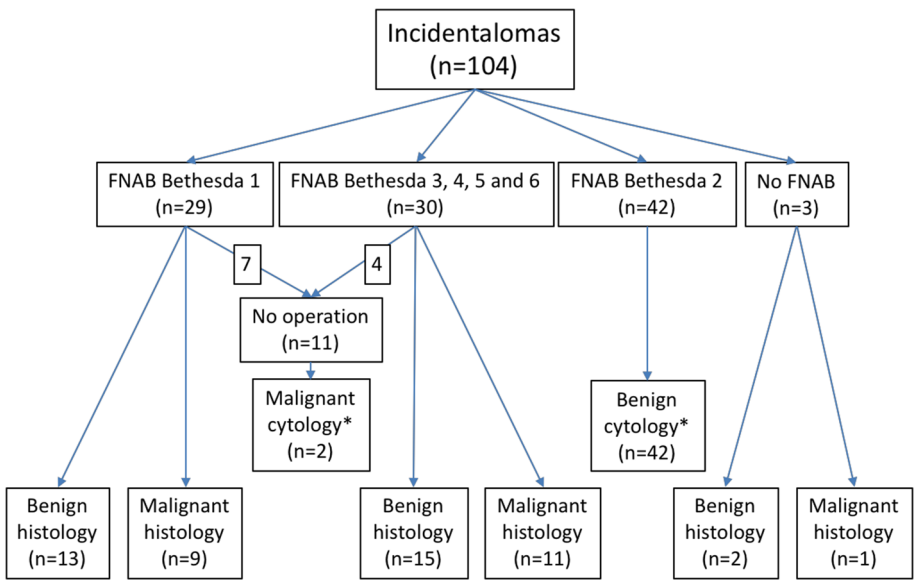

Fig. 1 Flowchart. FNAB: Fine-needle aspiration biopsy. *Conclusive cytology: Benign cytology = Bethesda 2. Malignant cytology = Bethesda 6

Table 3 Histological and cytological diagnosis of malignant incidentalomas

	n
Histological diagnosis	
Papillary carcinoma	17 (68%)
Follicular carcinoma	3 (12%)
Metastasis from clear cell adenocarcinoma	1 (4%)
Cytological diagnosis	
Metastasis from sarcoma	1 (4%)
Metasis from lung cancer	1 (4%)

the literature. Several studies, mostly retrospective ones, have estimated the risk of malignancy in FFTI from eight to 66%. This is much higher than the 5% risk of malignancy in incidental nodules found on US [20]. The question is, whether all FFTIs should be surgically removed due to a substantial risk of cancer or if it is possible to stratify the patients based on US and FNAB. Knowledge about risk of malignancy based on solid prospective cohorts is needed and a standardized strategy for the management of FFTI is warranted.

To our knowledge, this is the first study to use prospective data from a fast track HNC program to estimate the risk of malignancy in FFTIs. We included an unselected group of patients with FFTI referred to the HNC fast track program at our tertiary HNC center. In addition, our results included cytology of almost all FFTIs (101/104) and the histopathological diagnoses in around half of the cases (51/104).

Our study suggests that the risk of malignant thyroid disease in FFTI is 24%. As expected, most of the patients with malignant histology had papillary carcinoma. This is consistent with the histology of thyroid cancers in the general population [22]. The probability of the lesion being benign was estimated to 76% (32% benign histology and 44% benign cytology).

In a group of 304 patients with FFTI, Hagenimana et al. [6] found a risk of malignancy of 8.2%. However, cytology and histology were missing in a significant part of the included patients. In a recent prospective study by Thuillier et al. [23], the malignancy was 17% which is closer to our findings. However, FNAB was only performed in about one-third of the patients, and a histology diagnosis was only present in 19 out of 92 cases, potentially leading to an underestimation as well.

In eleven patients, we were not able to classify the risk because these patients did not have surgery. As stated in the results, two of the patients had disseminated cancer with metastatic lesions from lung cancer or sarcoma and could not undergo thyroidectomy due to the primary cancer disease. Due to the FNAB showing conclusive cytology suggesting malignancy (Bethesda 6), they counted in our final analysis of malignancy rate. In other three patients, thyroidectomy was not performed because of the lesion being less than 10 mm or biochemistry was consistent with Hashimotos disease. US did not show any sign of suspicion to malignancy and the physicians decided not to proceed with surgery.

The American Thyroid Association Management Guidelines from 2015 suggest that FFTIs $\geq$ 10 mm should be further examined with FNAB [17]. If the nodule is smaller than 10 mm, the guideline recommends follow-up depending on the US. Our results show that US characteristics have a relatively low sensitivity for predicting cancer. However, the specificity ranges from 69 to 97% for the individual characteristic. The only statistically significant US characteristic to predict malignancy was the appearance of irregular margins with a sensitivity of 47%, specificity of 96%, PPV 78%, and NPV 85% ($p < 0.005$). This indicates that the diagnosis cannot solely rely on US, because cancers would be missed. On the other hand, US is a sensitive examination for the experienced clinician, and the absence of sonographic suspicious features is a good indicator of benign disease.

Additionally, we found 27% of the lesions smaller than 10 mm to be malignant. However, it is known from previous studies that active surveillance of thyroid cancers smaller than 10 mm is favorable [24, 25]. Very few (<5%) increase in size and the prognosis does not get worse with time [24, 25]. Hence, it can be argued that FFTIs <10 mm should be further examined only with US and not FNAB. In case they present malignant characteristics on the US, they should be followed.

A weakness of our analysis of the US characteristics is observer variation, as there are no strict rules on how an irregular margin looks like, and when the echo density of a lymph node is suspicious. Therefore, definition and interpretation of US features may vary among examiners. We used paper forms to systematize the US examinations as much as possible. However, no observer variation studies were performed.

Another limitation may be that we did not achieve histological confirmation in all patients. Cytology was used as proxy for histology in a substantial part of the series. However, to do surgery in cases with benign cytology is difficult to defend in an ethical perspective.

Also, the fact that we were not able to secure that the nodule found by PET/CT was the same as the one found by US and finally that the histological diagnosis was based on the nodule in question. Theoretically, the malignant diagnosis could have been made on another nodule than the FFTI. We tried to reduce the variation by having the PET/CT scan available on the computer screen when we did US and FNAB. Also, our pathologist tried to give a precise description of the localization of nodules in the specimen.

Despite of the prospective design of our study, selection bias cannot be ruled out. There may be patients with FFTI from our referral area who do not reach our HNC fast track program. Consequently, we are not able to determine any demographic incidence of FFTI.

Finally, it is worth mentioning that PET/CT alone cannot rule out malignancy. Especially in iodine-deficient areas, as Denmark, unnecessary operations can be prevented, if a thyroid scintigraphy is performed prior to FNAB. It is well known that "warm" autonomous nodules have an extremely low risk of malignancy [26]. Due to our time limits in our fast track setting, it has not been possible to include the scintigraphy in the work-up.

Conclusion

This study shows that a FFTI is malignant in 24% of the cases in a HNC fast track setting. FNAB and US are useful to rule out malignancy. The appearance of irregular margins on US is specific for malignancy with NPV of 85% and specificity of 96%. If the cytology on FNAB is categorized as Bethesda 1, 3, 4, 5, or 6, lobectomy is advised to rule out cancer.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Informed consent Informed consent was obtained from all individual participants included in the study.

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