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RESEARCH ARTICLE

Specificity and Sensitivity of Combined (99m)Tc-Methoxy-Isobutyl-Isonitrile Thyroid Scintigraphy and Fine Needle Aspiration Cytology (Fnac) in A Self-Selected Sample

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Abstract

Background: The prognostic ability to detect malignity in thyroid nodules is far from being perfect so high numbers of chirurgical treatments are currently performed without final histological proof for malignant neoplasm. Technetium-99m methoxyisobutylisonitrile (Tc-MIBI) scan may help differentiate between benign and malignant thyroid nodules. However, it is still unclear how this method compares to other techniques already state of the art. This study was conducted to investigate the efficacy of Tc-MIBI scintigraphy in comparison with Fine-Needle Aspiration Cytology (FNAC) and a combination of both.

Patients and methods: This retrospective study was conducted on 342 patients in a german hospital with cold thyroid nodules greater than 1 cm in diameter as detected with Tc-pertechnetate(TCP)-scintigraphy. Uptake of MIBI in thyroid nodules was compared with that in the surrounding normal thyroid tissue for both early and delayed images 10 and one hour after intravenous injection of 500 MBq. 248 patients underwent fine-needle aspiration biopsy (FNAB). Finally, the results of both methods were combined with cytological clinical findings.

Results: 236 male and 106 female patients in the study with a mean age of 51 years (± 11.5 years) were enrolled. 57 patients received a histopathological diagnosis after thyroid surgery and were included for further analysis. Sensitivity of (99m)Tc-MIBI scans reached over 81% and specificity was 17%. Both (99m) Tc-MIBI scan and fine needle aspiration biopsy reached a high and comparable negative predictive value of around 80%. The corresponding positive predictive value was slightly higher in the FNAB group (25% vs. 19%). The combined approach of (99m)Tc-MIBI scan and fine needle aspiration cytology led to higher sensitivity (91%) and specificity (70%).

Conclusion: The study demonstrated that (99m)Tc-MIBI scanning may be useful in combination with other diagnostic techniques in patients with cold thyroid nodules. The availability of (99m)Tc-MIBI scanning, its low cost and easy application seem to be very promising in routine detection of cold thyroid nodules.

Keywords:

(99m)Tc-MIBI scan; Fine needle aspiration cytology; Thyroid nodules; Malignancy; Sensitivity; Specificity; Negative predictive value; Positive predictive value

Introduction

The prevalence of thyroidal nodules amounts to 20 –25% of the adult population in Germany [1-4]. But the probability of malign nodules is approximates only 0.05 %[5]. Since the prognostic ability to detect malignity beforehand is far from being perfect high numbers of operations are currently

performed based merely on safety grounds which leads to a considerable higher frequency of chirurgical treatment in Germany as compared to other countries e.g. the average frequency in Germany has been around one per 750 capita (England: 1 OP/6.000, USA 1 OP/4.901) [5].

A scintigraphically detected "cold" nodule may often be further examined for malignancy by MIBI-scintigraphy. (^{99m})Tc-MIBI is a lipophil cation complex which can be up-taken in the blood and tissues. Dual or planar imaging of the uptake in reference to the surrounding paranodular thyroid tissue is used for the diagnostic evaluation of malignancy (Mezosi, Sathekge) An enrichment of (^{99m})Tc-MIBI in cold nodules indicates a "mismatch" which increases the probability of true malignancy of the nodules under consideration up to 66% [6]. No enrichment in the nodule ("match") is highly associated with a true negative diagnosis.

The most important prospective method to evaluate the dignity of a thyroidal nodule is up to now Fine Needle Aspiration Biopsy (FNAB) but at least 20 % of the probes are not diagnostically valid. Clinical findings are in 7-28 % false negative compared to the gold standard to detect malign nodules, the histological diagnosis after surgery.

This study assesses sensitivity of and specificity (^{99m})Tc-methoxy-isobutyl-isonitrile ((^{99m}))Tc-MIBI) thyroid scintigraphy, fine needle aspiration cytology and a combination of both in a german sample in

Sinceabout 55-85% of those undergoing surgery do not have thyroid cancer at final histology diagnosis Campennì et al [7]. Evaluated prospectively the role of (^{99m})Tc-methoxy-isobutyl-isonitrile thyroid scintigraphy in differentiating malignant from benign thyroid nodules with indeterminate cytology. The overall sensitivity and specificity of (^{99m})Tc-MIBI quantitative analysis in identifying patients with malignant lesions was 100% and 90.9%, respectively.

Yordanova et al. [8] found that the most valuable feature of (^{99m})Tc-MIBI scintigraphy is its Negative Predictive Value (NPV). With the appropriate image interpretation method a high sensitivity (91%) and high specificity (91%) could also be surveyed.

The study of Sharma et al [9]. Investigated 77 patients with cold nodules which underwent a (^{99m})Tc-MIBI-scintigraphy and were histologically diagnosed after surgery. 33 patients were found with adenoma from which 28 patients showed a mismatch based on (^{99m})Tc-MIBI scintigraphy. Sensitivity, specificity and positive predictive value were 84.4%, 95.45% and 93.33%, respectively.

A recent meta-analysis included twenty-one studies with regard to the prognostic ability of (^{99m})Tc-MIBI scans. Pooled sensitivity and specificity in detecting malignant thyroid nodules were 85.1 % [95 % confidence interval (95 % CI): 81.1-88.5 %] and 45.7 % (95 % CI: 42.7–48.7 %). They concluded that (^{99m})Tc-MIBI scan is a sensitive diagnostic tool in predicting the malignancy of thyroid nodules. On the other hand, (^{99m})Tc-MIBI uptake did not seem to correlate highly with the histologic subtypes of malignant neoplasm (papillary, follicular, medullary) and was not specific for primary thyroid malignancy. A significant increase in specificity (from 45.7 to 62.8 %) has been be noticed when the analysis of diagnostic performance was restricted to "cold" thyroid nodules [6].

Material and Methods

Study population

In this retrospective observational study we aimed at the evaluation of malignity in patients with one or more hypofunctional thyroid nodules. We investigated 342 patients enrolled in the study between Oktober 2012 and Oktober 2016 which underwent (^{99m})Tc-MIBI scan (n=342) and fine needle aspiration biopsy (FNAB, n=284).

All enrolled patients had at least a known „cold" thyroid nodule and were eligible for chirurgical surgery but admitted themselves for a further diagnosis in our hospital before their decision to perform the operation was made.

57 patients received a histopathological diagnosis after thyroid surgery and were included for further analysis, the gold standard to detect malign nodules.

The mean age of the patients was 51 years (± 11.5 years) with 236 male and 106 female patients enrolled.

The local ethics committee of our university approved prospective study; informed consent was obtained from all participants.

(^{99m})Tc-MIBI thyroid scintigraphy

All patients underwent TPT-scintigraphy followed by MIBI-scintigraphy. After intravenous injection of MIBI (standard dose 500 MBq) we used a dual-phase protocol with planar images approximately 10 min post-injection (p.i.) and one hour post injection. The uptake in the examined nodule was compared with the paranodular thyroid tissue. A correlation with the TPT-scintigraphy showed either a "match" (i.e., concordant decreased uptake of both tracers) or a "mismatch" (i.e., cold nodule with increased MIBI-uptake).

Fine needle aspiration biopsy (FNAB)

284 patients underwent a FNAC. The biopsy was through guided ultrasound using a 20-gauge needle attached to a 20 ml Cameco syringe-pistol. Smears were made and air-dried slides were stained with hematoxylin-eosin. The remaining aspirate material in the syringe was rinsed with 0.9% sodium chloride. The fluid material was centrifuged, the sediment was smeared and slides were prepared. Adequacy of the aspirates was assessed on the basis of the guidelines of the Papanicolaou Society [32].

Statistical analysis

Specificity, sensitivity; PPV, NPV as well as Cohen's Kappa (Cohen) had been calculated to compare (99m)Tc-MIBI thyroid scintigraphy and fine needle aspiration biopsy (FNAB). Statistical significance was assumed at the 95% confidence level.

Results

In the entire sample of 57 patients were 11 nodules histologically

Table 1: Sensitivity, Specificity, PPV and NPV, MIBI and histology (nodules).

		Histology (n)	
		malign	benign
(99m)Tc-MIBI (n)	mismatch	9	38
	match	2	8
		Sensitivity: 81.82% [44.22%. 97.72%]	Specificity: 17.39% [7.82%. 31.4%]

Table 2: Sensitivity, Specificity, PPV and NPV, FNAB and histology (nodules).

		Histology (n)	
		malign	benign
FNAB (n)	positive	4	12
	negative	5	19
		Sensitivity: 44.44% [13.7%. 78.8%]	Specificity: 61.29% [42.19%. 78.15%]

Table 3: Sensitivity, Specificity, PPV and NPV, MIBI/FNAC and histology (nodules).

		Histology (n)	
		malign	benign
(99m)Tc-MIBI/FNAC (n)	positive	10	44
	negative	1	90
		Sensitivity: 90.91% [58.72%. 99.77%]	Specificity: 70.31% [61.6%. 78.08%]

diagnosed as macro-follicular and micro-follicular adenoma which amounts to a prevalence of 19.3%. As table 1 shows, 9 of 11 nodules were identified as mismatch in the (^{99m})Tc-MIBI thyroid scintigraphy scan and among 38 histologically benign probes were 38 mismatches. Altogether we found 10 matches from which were two malign nodules. The positive predictive value for a malign nodule therefore was low (19%) whereas the negative predictive value had been comparably higher: The probability to identify a benign nodule (match) was 80%. Sensitivity of (^{99m})Tc-MIBI scans reached over 81% and specificity was 17% (Table 1).

Compared to the nodules with FNAB detection (table 2) the PPV was a little higher than nodules diagnosed with (^{99m})Tc-MIBI scans (25%) whereas the NPV was the almost the same (79%). Sensitivity was comparably lower for the nodules diagnosed with FNAB (44%) and specificity more than threefold higher compared to the (^{99m})Tc-MIBI scans (61%)

We then combined the (^{99m})Tc-MIBI scans with the corresponding results of FNAB plus the cytological evaluation of malignity in the nodules in our sample. This combined methodology gave rise to a comparably higher NPV (99%) and to higher sensitivity (91%) and specificity (70%) as table 3 shows.

Finally, we computed Cohen's Kappa as indicator for the degree of association between two distinct measurements. Cohen's Kappa in the sample diagnosed with FNAB and (^{99m})Tc-MIBI scan amounted to 0.195 [95%-CI: 0.079-0.312) which we considered as relatively low in that both detection methods differed remarkably in their prognostic ability to detect malign nodules.

Discussion

The present study aimed at the comparison of different detection methods to identify malign thyroidal nodules. Both (99m)Tc-MIBI scan and fine needle aspiration biopsy reached a high and comparable negative predictive value of around 80%. The corresponding positive predictive value was slightly higher in the FNAB group (25% *vs* 19%).

This was in line with the study of Boi et al. [11] which showed no evidence of a superior detection of malign nodules with (^{99m})Tc-MIBI scintigraphy as opposed to FNAC with a sensitivity of 93 % and specificity of 70%. No significant difference in MIBI related positivity was found between malignant (67%) and benign (56%) nodules whereas the ability to differentiate between histological HC tumors and oncocytic metaplasia with a specificity of 60% and a sensitivity of 79% was better.

Sensitivity of (^{99m})Tc-MIBI scan in detecting malignant thyroid nodules in our sample was 80% and 17%, respectively, which was close to the pooled analysis in the meta analysis of Treglia et al. [6] Specificity of (99m)Tc-MIBI scans in our study was considerably lower (17.4% *vs* 45.7%) which points to a lower ability to correctly identify benign nodules.

The observed low agreement between the both detection method of FNAB and (^{99m})Tc-MIBI scan in our sample may at least partly been due to the relatively demanding task of judging the scintigraphs correctly as match or mismatch [12,13]. A recent study which compared the intra- and interrater reliability of scintigraphic imaging showed that intraobserver agreement ranged from K=.56 - .78

(Cohen's Kappa) which is moderate [14,15]. Interobserver agreement was considerably lower (K=.44-.53, Fleiss' Kappa) and indicated the complexity and variability of the judging which may lead to incorrect classification and was dependent upon the experience of the rater [12]. Quantitive evaluations as well as SPECT-techniques have recently proposed [16,17].

We are also aware of the fact that due to the retrospective perspective of this study it cannot be ruled out that selection bias occurred with regard to different patient characteristics in the group with surgery as compared to the MIBI or FNAB- groups not being eligible for chirurgical treatment.

Self-selection bias may also took place since the all enrolled patients in this study choose our university ambulance by themselves (self-admittance) which may introduce a self-selection bias.

This self selection bias is also known as healthcare access bias or centripetal bias [18]. Sensitivity, specificity and other measures of accuracy will be dependent upon the population in which the test or measure is applied [19]. Self-selection bias may lead to a more favorable outcome of the diagnosis methods and may enhance specificity and sensitivity. Because patients self referred to (99m) Tc-MIBI scan, they may have had a higher likelihood of thyroid malignancy than those who are not which in turn may influence sensitivity and specificity [20] and would possibly inflate sensitivity and specificity rates. Accuracy measures may also be underestimated as difficult prognosis in many cases may lead to poorer detection rates compared to a general sample of patients under scrutiny.

A prospective study will be necessary to take selection bias into account. On the other hand did our sample not differ substantially in its patient characteristics when compared to other studies aiming at the evaluation of detection methods for thyroidal malignancy.

Other detection methods have to be taken under consideration as the accuracy of FDG-PET/CT in detecting thyroid malignancy was higher than that of (^{99m})Tc-MIBI scan as Piccardo et al. [21] demonstrated. A recent meta-analysis on emission tomography using FDG (FDG-PET) in thyroid nodules with indeterminate cytology reported a pooled sensitivity and specificity of 95% and 48%, respectively [22].

On the other hand the combined prognosis with (^{99m})Tc-MIBI scan and FNAC in our sample increased sensitivity and specificity to 99% and 70%, respectively, which is in line with the results found in other studies where the combined approach of MIBI and FNAC increased the sensitivity in the MIBI positive group to 90% [11]. We therefore concluded that (^{99m})Tc-MIBI scan as single measure for the prognosis of malignant thyroid nodules has not been found sufficient but may reasonably combined with other prognostic methods as FNAC.

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