



Update in Thyroid and Parathyroid Imaging - Université Libre de Bruxelles 11.03.2023

Performance of nuclear imaging techniques in characterization of thyroid nodules

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Disclosure

Advisory Board and Research Support Roche Diagnostics

Agenda

- **Thyroid nodules: an appraisal**
- **Nuclear medicine techniques for thyroid nodules**
 - Thyroid scintigraphy with functional tracers
 - Thyroid scintigraphy with proliferation tracers
 - Positron emission tomography with ^{18}F - fluorodeoxyglucose (FDG)
- **Conclusions**
- **Q&A**

Epidemiology

- Thyroid nodules are very common
 - ▣ Palpable nodules
 - 5% of women
 - 1% of men
 - ▣ Ultrasound series
 - 19-67%
 - ▣ Autopsy series
 - 37-57%
- The prevalence of nodules increases with age
- Prevalence in women 1.5-1.7 times higher than men

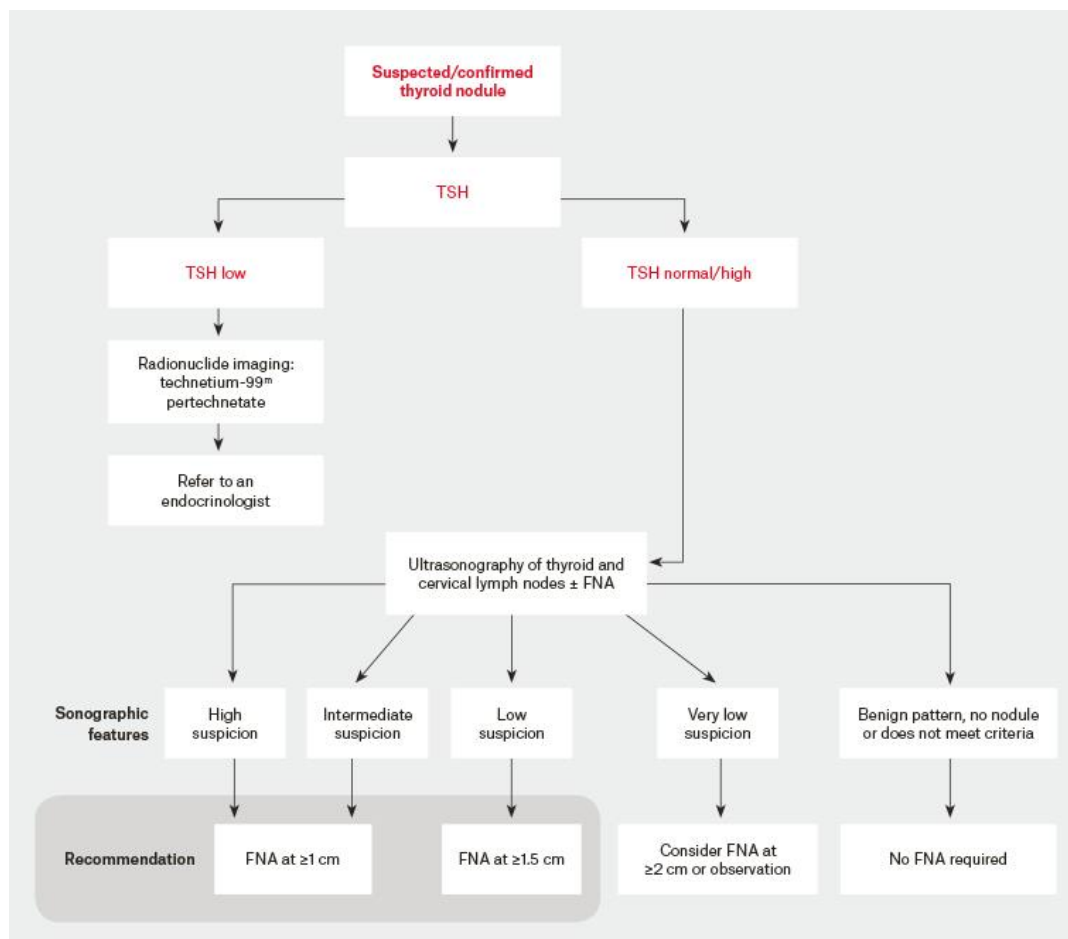
Clinical points

- How do patients with thyroid nodules present?
 - ▣ Nodule noted by patient
 - ▣ Nodule noted on routine physical
 - ▣ Nodule discovered incidentally on imaging
 - Carotid doppler U/S
 - Neck CT
 - ^{18}F FDG-PET scan
 - Etc
 - ▣ Obstructive symptoms

Malignant nodules

- Thyroid cancer occurs in 5-15% of thyroid nodules, and rate depends on risk factors
- Types of thyroid cancer
 - Differentiated
 - Papillary
 - Follicular
 - Medullary
 - Anaplastic
- Incidence of thyroid cancer is increasing
 - 1973: 3.6 per 100,000
 - 2009: 8.7 per 100,000
- Rise in incidence mostly attributed to papillary thyroid cancer and tumours < 2cm in size

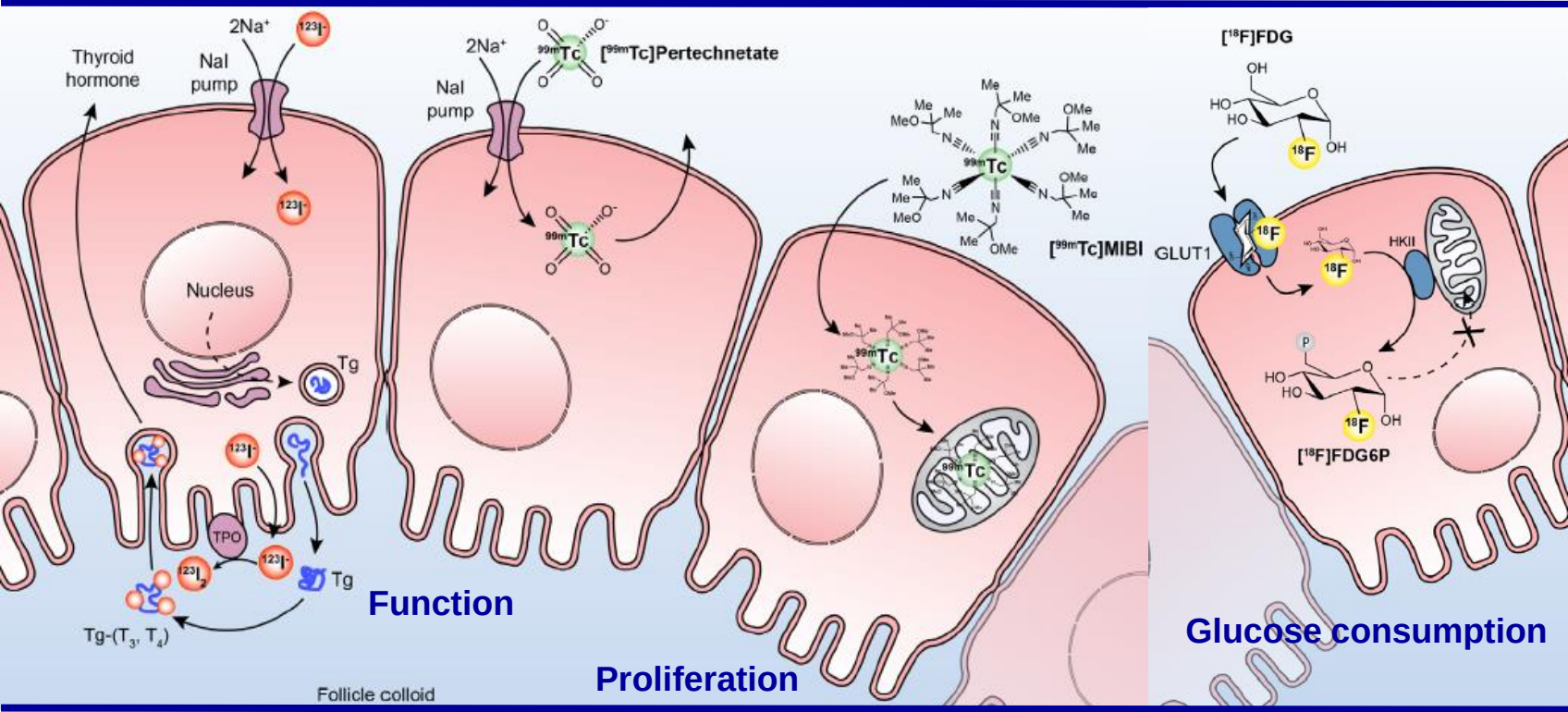
Thyroid nodules: diagnostic approach



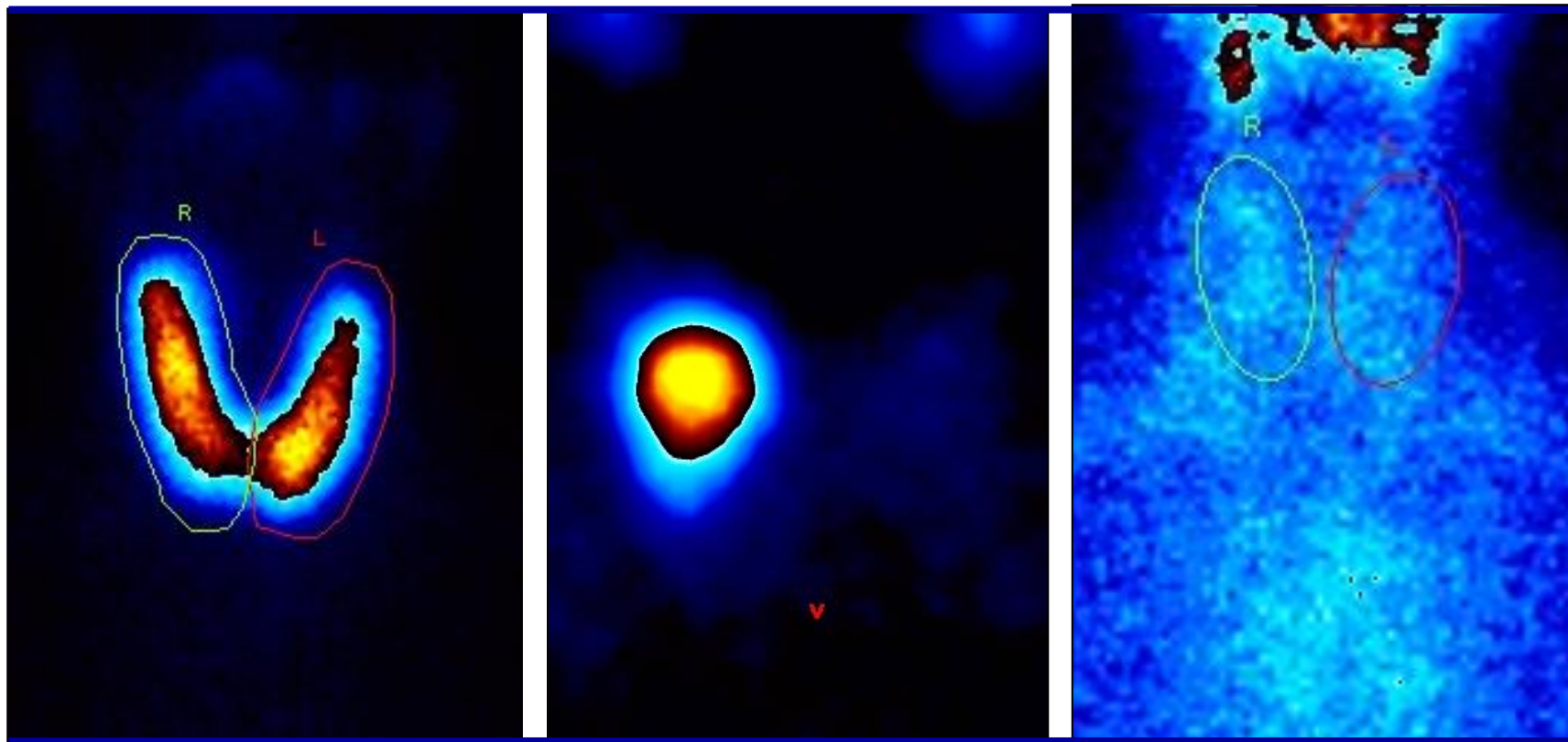
Thyroid scintigraphy: functional radiopharmaceuticals

[^{99m}Tc-pertechnetate, I-123]

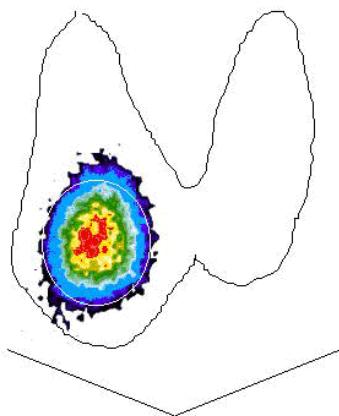
Thyroid radiopharmaceuticals



Thyrotoxicosis



Thyroid scintigraphy and FNAC



ETA 2006 Any solitary thyroid nodule (≥ 1 cm) should be **submitted to cytology unless proven to be hyperfunctioning**.

ATA 2015 Since **hyperfunctioning nodules** rarely harbor malignancy, if one is found that corresponds to the nodule in question, **no cytologic evaluation is necessary**.

AACE/AME/ETA 2010 Nodules that are **hot on scintigraphy** should be **excluded from FNA biopsy**.

Are all AFTNs associated to low-suppressed TSH values?

TSH measurement is not an appropriate screening test for autonomous functioning thyroid nodules: a retrospective study of 368 patients

Rayan Chami¹, Rodrigo Moreno-Reyes² and Bernard Corvillain¹

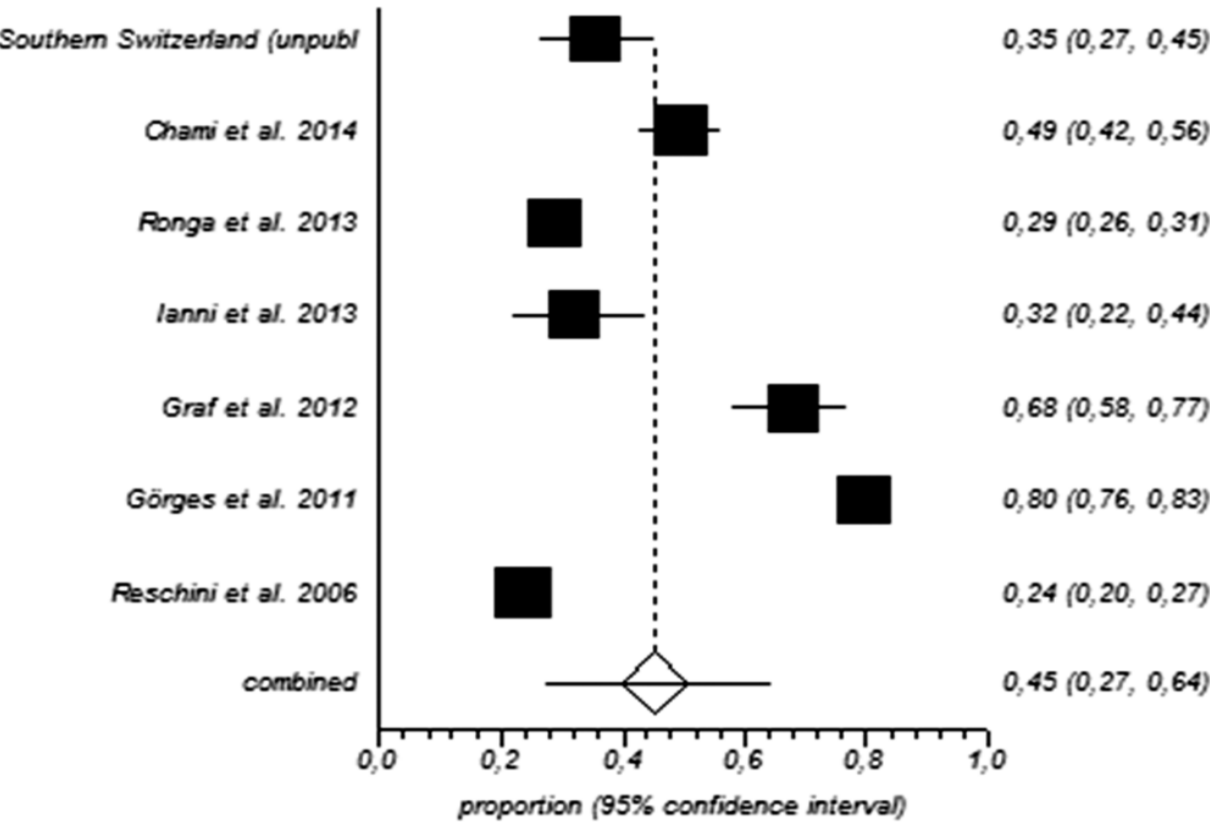
Departments of ¹Endocrinology and ²Nuclear Medicine, Hôpital Erasme, Université Libre de Bruxelles, route de Lemnik 808, 1070 Brussels, Belgium

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Table 2 Characteristics of AFTNs in patients of Group III (n=217) according to TSH level (< or ≥0.4 μU/ml). Except for TSH, values are means±s.e.m.

	TSH <0.4 μU/ml	TSH ≥0.4 μU/ml
No. of patients (%)	110 (50.7)	107 (49.3)
Sex ratio F:M	2.3 (77:33)	3.5 (83:24)
Age at analysis	54.4±1.4	53.3±1.4
Median (P25–P75) TSH value (μU/ml)	0.04 (0.04–0.13)	0.91 (0.70–1.34)
Main diameter of the nodule (mm)	33.03±1.15	24.66±1.10 ^a
Volume of the nodule (ml) ^b	11.32±1.38	5.31±0.70 ^a
Circumstances of diagnosis: thyroid dysfunction-nodule-unknown	63/35/12	11 ^c /87/9 ^d

Proportion of patients with AFTN and normal TSH [random effects]



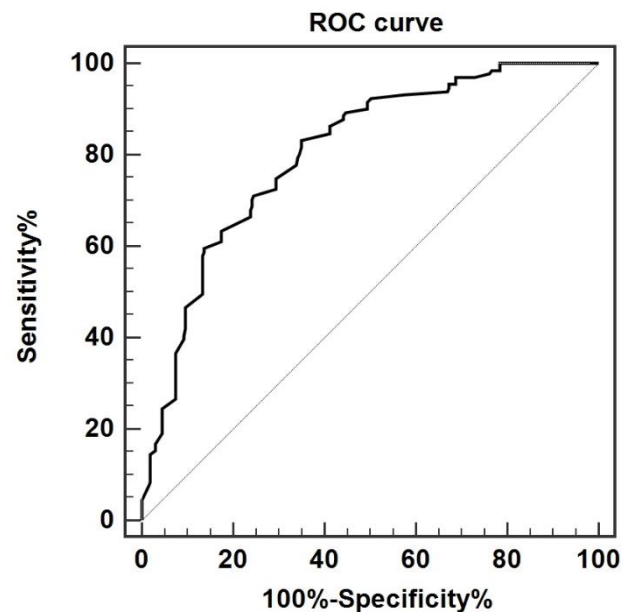
Treglia et al. Eur J Clin Invest 2015

496 patients

- Thyroid nodule > 10 mm
- 45 with TSH <0.40 mUI/L
- 406 with TSH 0.40-4.00 mUI/L

Thyroid scintigraphy

- ❑ **173 (38%) AFTN**
 - 36/45 (80%) with reduced TSH
 - 137/406 (34%) with normal TSH
 - AFTN-TSH 1.00 [<0.1 -2.38] mUI/L
 - nAFTN-TSH 1.60 [0.40-4.00] mUI/L

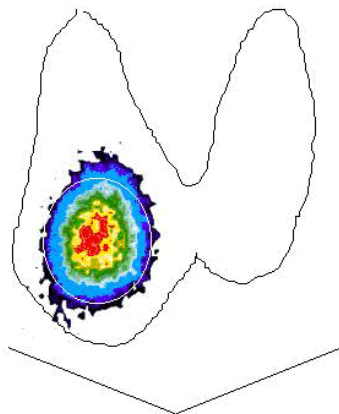


AUC 0.804 (CI: 0.761-0.842)]

- **TSH 1.49 mIU/L** [i.e., sensitivity 83%, specificity 83% , +PV 65%, -PV 88%].
- **TSH 2.38 mIU/L** [i.e., sensitivity 100%, specificity 21%, +PV 40% and -PV 100%].

Giovannella et al. Endocrine 2016

Thyroid scintigraphy and FNAC



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ATA 2015 Since **hyperfunctioning nodules** rarely harbor malignancy, if one is found that corresponds to the nodule in question, **no cytologic evaluation is necessary.**

AACE/AME/ETA 2010 Nodules that are **hot on scintigraphy** should be excluded from **FNA biopsy.**

Are all AFTNs ultrasonographically benign (benign or low risk TIRADS)?

Risk Stratification of Thyroid Nodules Using the Thyroid Imaging Reporting and Data System (TIRADS): The Omission of Thyroid Scintigraphy Increases the Rate of Falsely Suspected Lesions

Simone Schenke, Philipp Seifert, Michael Zimny, Thomas Winkens, Ina Binse and Rainer Gorges

Journal of Nuclear Medicine March 2019, 60 (3) 342-347; DOI: <https://doi.org/10.2967/jnumed.118.211912>

615 hyperfunctioning thyroid nodule

- Patients 582 (f 442, m 140)
- Diameter 23.2 ± 10.0 mm)

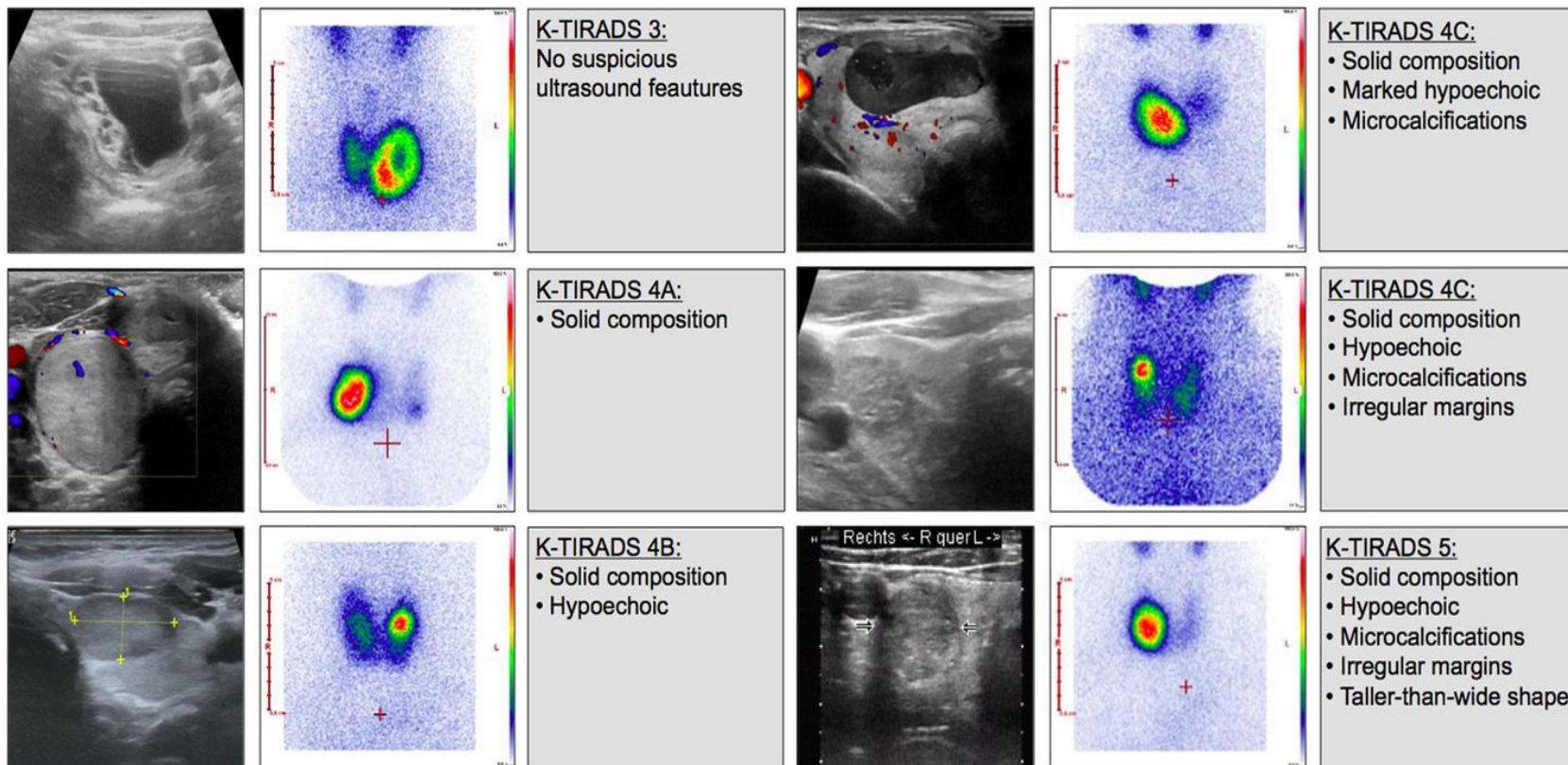
US-Thyroid Imaging Reporting and Data System (TIRADS)

- 15.9% TIRADS ≤ 3
- 29.3% TIRADS 4A
- 29.3% TIRADS 4B
- 24.9% TIRADS 4C
- 0.10% TIRADS 5

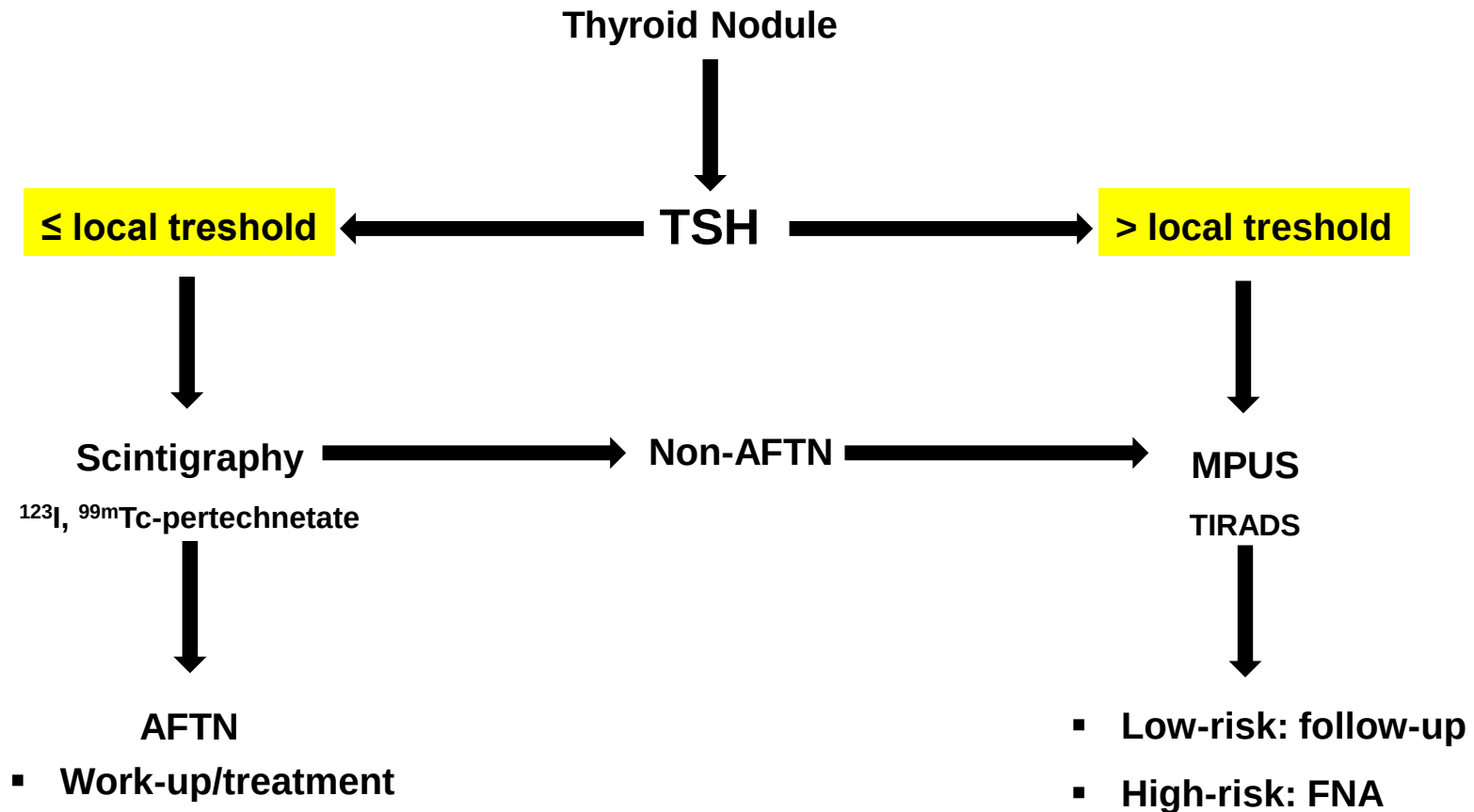
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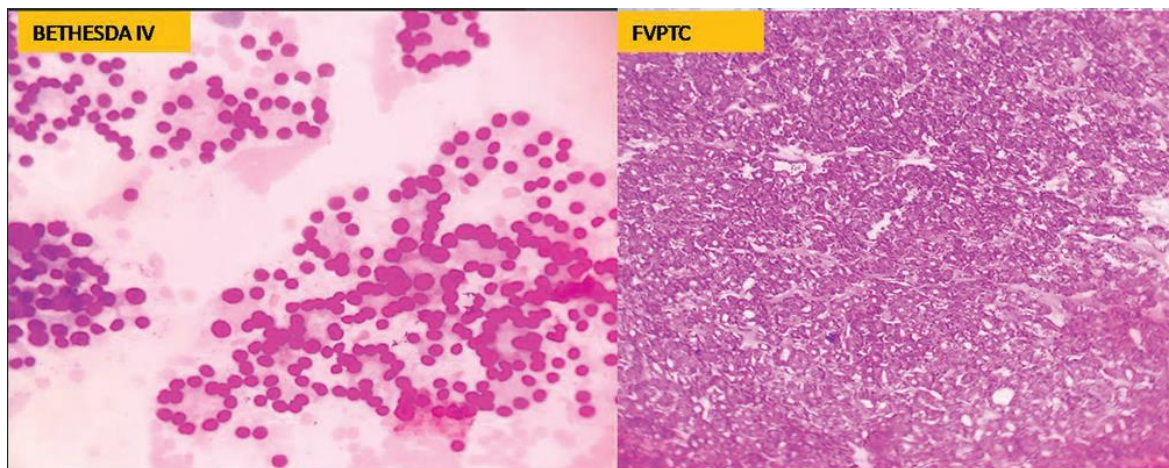
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Proposal: adapt locally the TSH threshold for thyroid scintigraphy



Cytologically indeterminate thyroid nodules

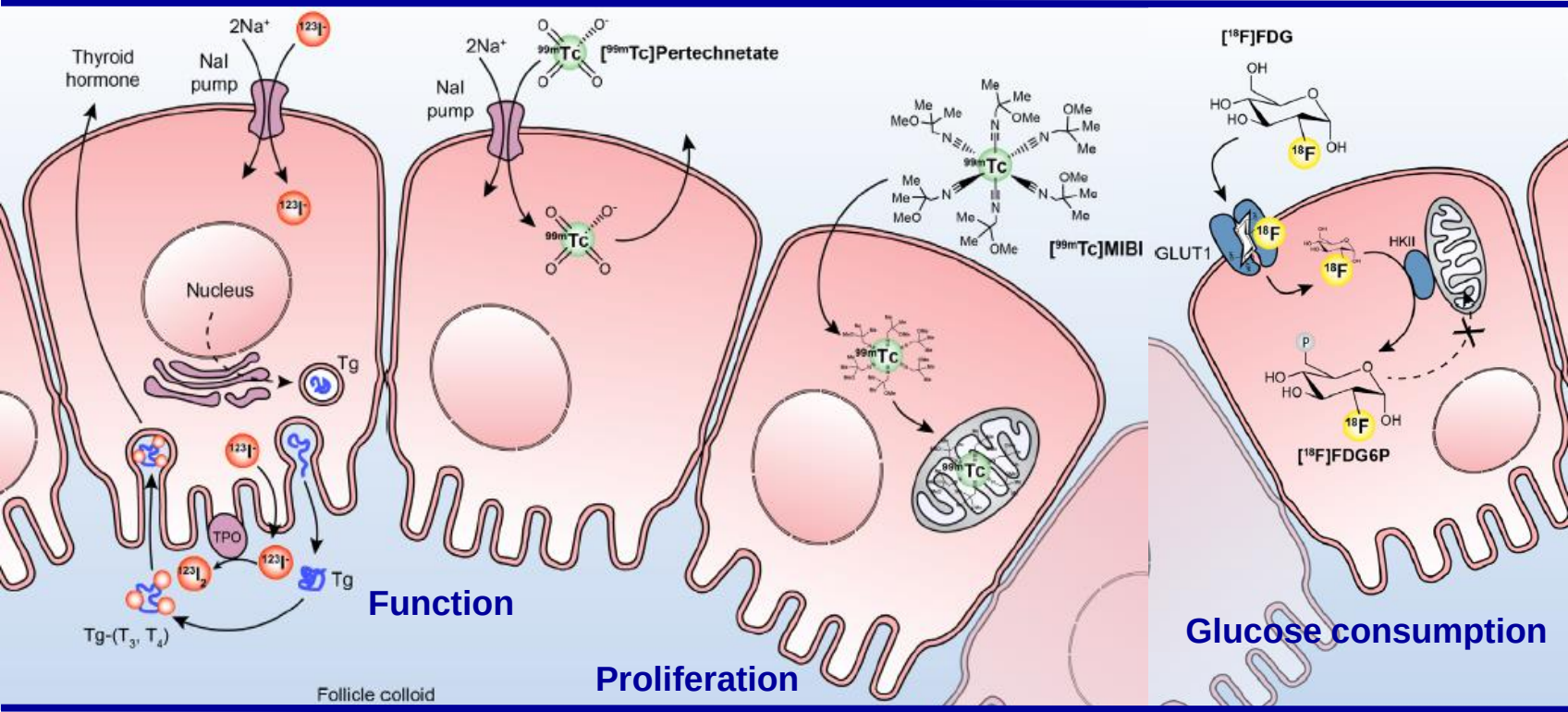


- Indeterminate thyroid cytology (Bethesda category III and IV) corresponds to follicular-patterned benign and malignant lesions, which are difficult to differentiate on cytology alone
- Approximately 25% of indeterminate thyroid nodules harbor malignancy
- The value of additional diagnostics is best defined by end points such as desired minimal rates of accurately prevented unbeneficial surgeries (rule-out capacity) or accurately diagnosed carcinomas (rule-in capacity)
- None of the diagnostic techniques currently available has near-perfect sensitivity, near-perfect specificity, and cost-effectiveness
- A multimodal stepwise approach using a sensitive rule-out and specific rule-in test might offer the most conclusive diagnosis for indeterminate thyroid nodules
- The decision favoring or opposing a certain diagnostic technique strongly depends on population-dependent variations in cytology (e.g., Hürthle cell cytology), tumor genetics and prevalence of malignancy, and on the costs and feasibility of the desired diagnostic in the local patient population

Thyroid scintigraphy: proliferation imaging

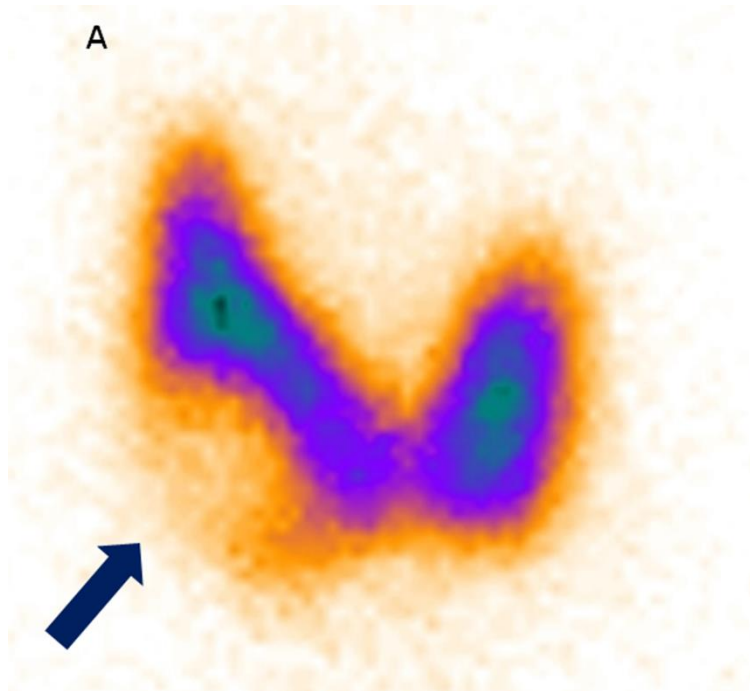
[^{99m}Tc-sestaMIBI]

Thyroid radiopharmaceuticals

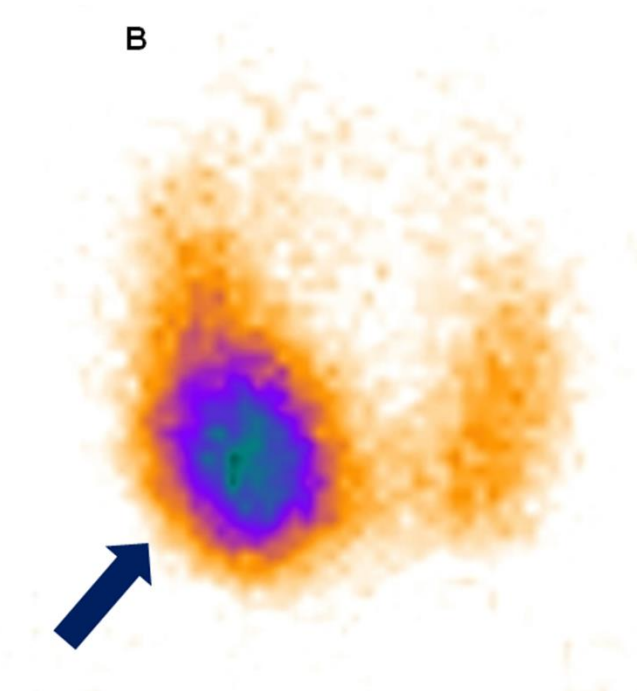


Thyroid scintigraphy [^{99m}Tc -sestaMIBI]

Cytologically indeterminate thyroid nodules (Bethesda III-IV, Thy 3, TIR3)



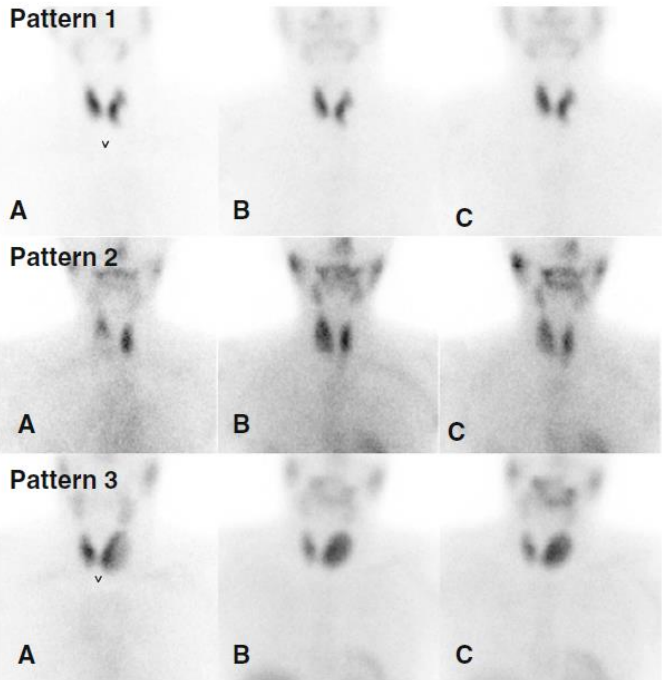
^{99m}Tc -pertechnetate



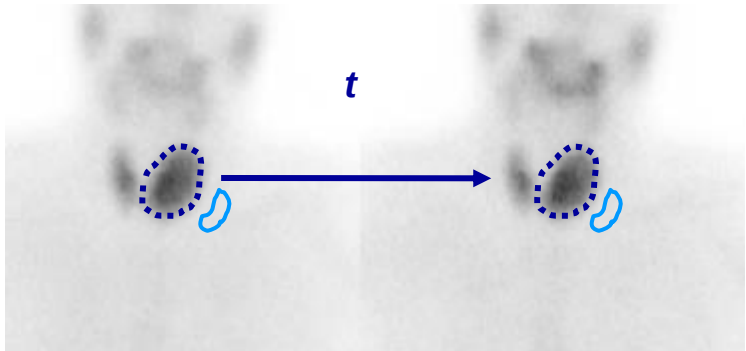
^{99m}Tc -sestaMIBI

Thyroid scintigraphy [^{99m}Tc-sestaMIBI]

Visual assessment



Washout index (WOInd) = $[(\text{delayed upt ratio}/\text{early upt ratio}) \times 100] - 100$



	Sens	Spec	Acc	PPV	NPV	+ LHR
MIBI visual	62%	95%	87%	83%	88%	4.56 1.94-9.54
MIBI WO _{ind}	100%	96%	98%	88%	100%	12.35 8.76-21.45
Biomarkers	25%	94%	80%	57%	77%	1.74 0.94-4.78

Giovannella et al. EJNMMI 2014

Diagnostic Performance of ^{99m}Tc-Methoxy-Isobuty-Isonitrile (MIBI) for Risk Stratification of Hypofunctioning Thyroid Nodules: A European Multicenter Study

Simone Agnes Schenke ^{1,2,*}, Alfredo Campenni ³, Murat Tuncel ⁴, Gianluca Bottoni ⁵, Sait Sager ⁶, Tatjana Bogovic Crcic ⁷, Damir Rozic ⁸, Rainer Gorges ⁹, Pinar Pelin Özcan ¹⁰, Daniel Groener ¹¹, Hubertus Hautzel ¹², Rigobert Klett ¹³, Michael Christoph Kreissl ² and Luca Giovannella ¹⁴

Inclusion criteria

- a. age $\geq$ 18 years,
- b. hypofunctioning TN of at least 10 mm in maximum diameter,
- c. EU-TIRADS risk class 4 (intermediate-risk) or 5 (high-risk)
- d. MIBI imaging

and

-FNAC with indeterminate results (Bethesda classification III, IV, ICCRTC TIR 3A/B) with available histopathological results

or

-FNAC with benign results (Bethesda classification II, ICCRTC TIR 2) with either histopathological results or follow-up of at least 12 months without progression (not more than 3 mm growth in one diameter).

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12 centers

284 females (53.5 ± 13.3 years) and 74 males (53.2 ± 12.6 years; ($p = 0.618$))

365 TNs (max size median 25 mm (19/33 mm))

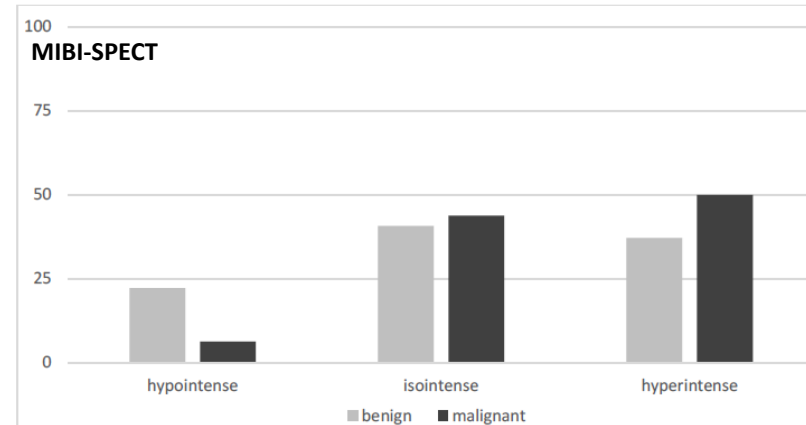
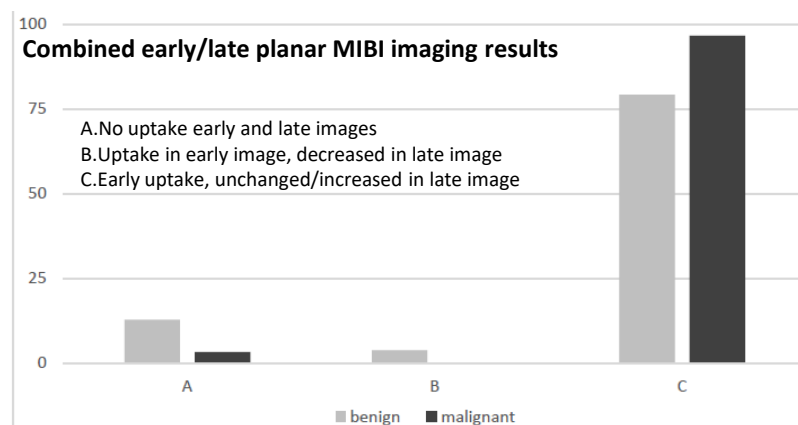
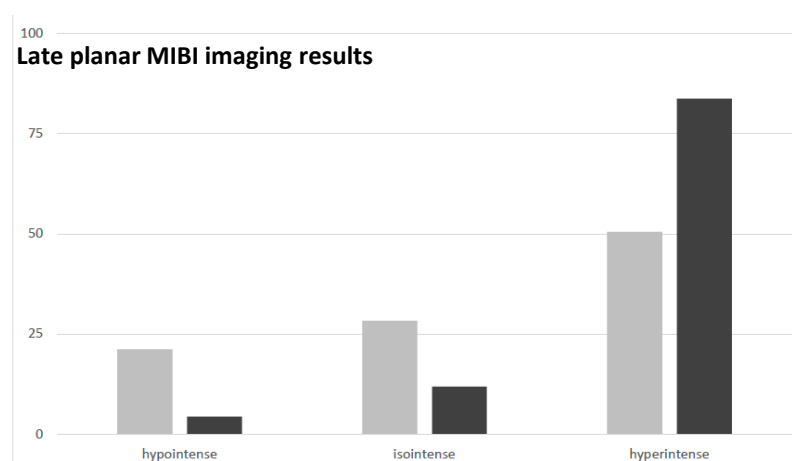
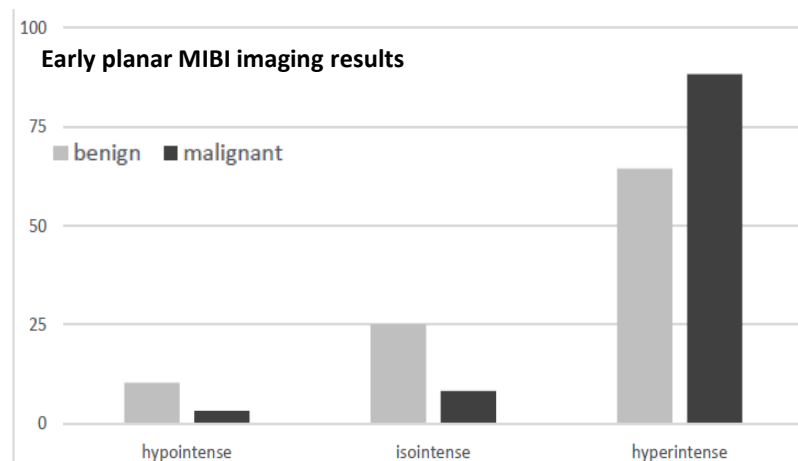
Benign, $n = 297$ benign

Malignant, $n = 68$

Article

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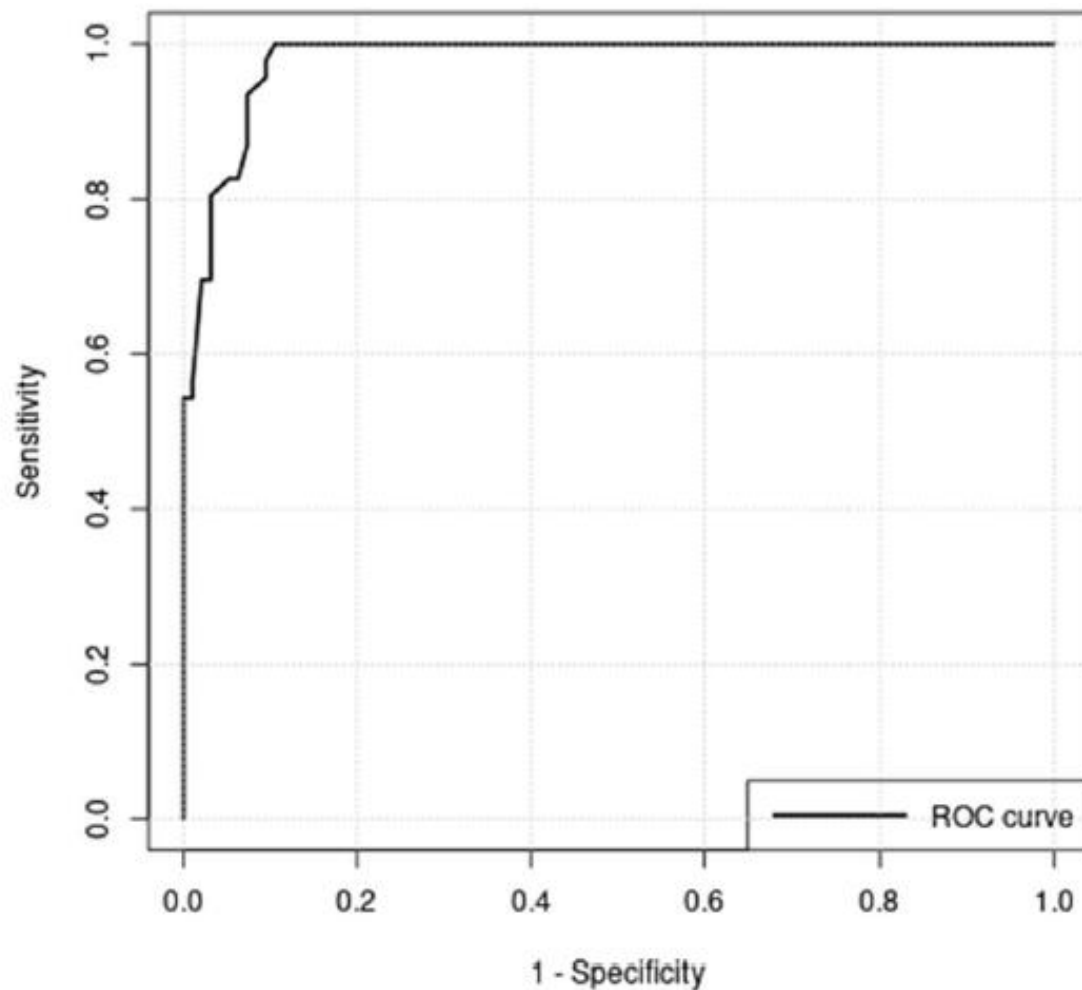


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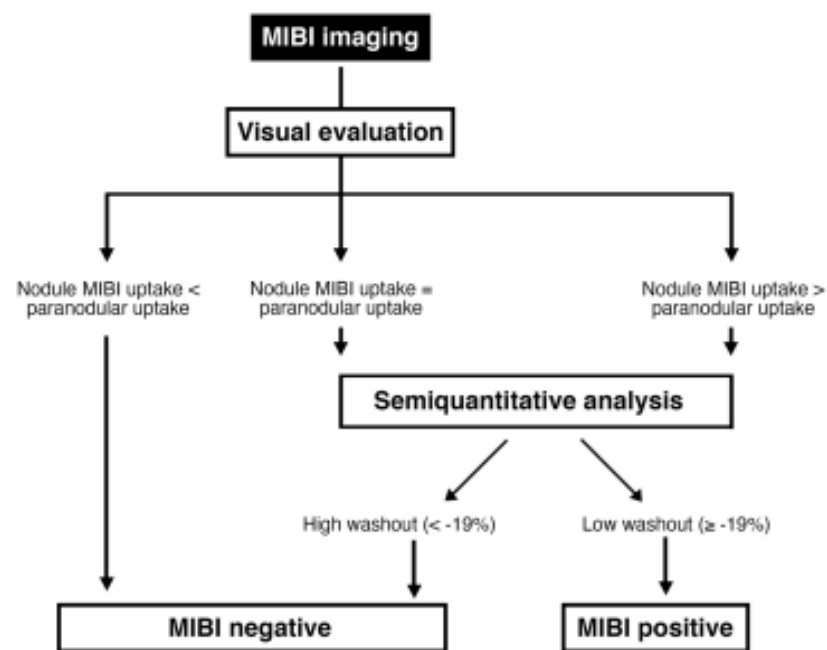
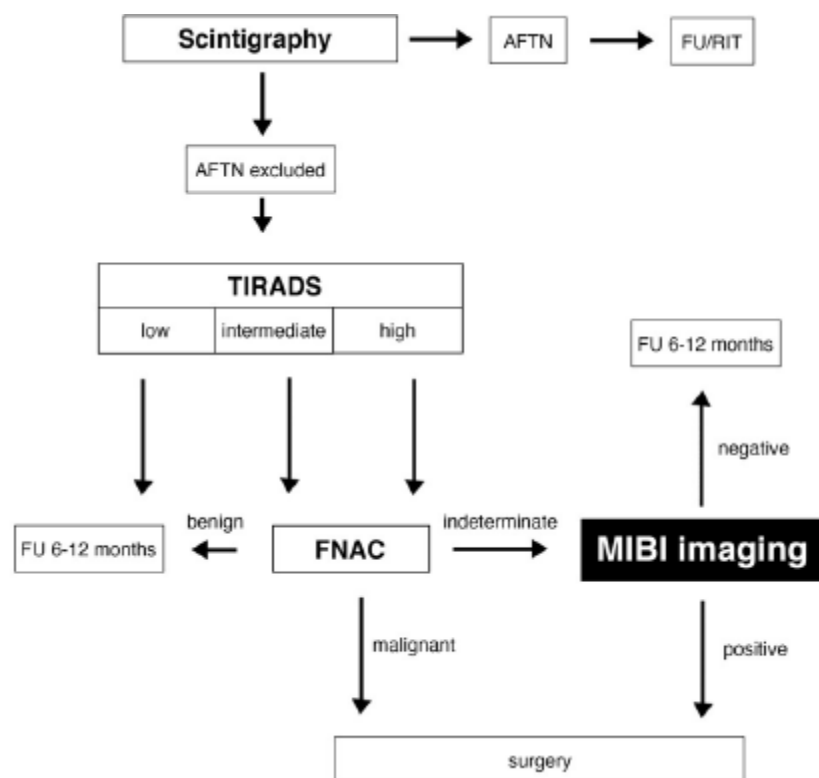
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Washout Index (cutoff -19%)
Area under Curve (AUC) = 0.980



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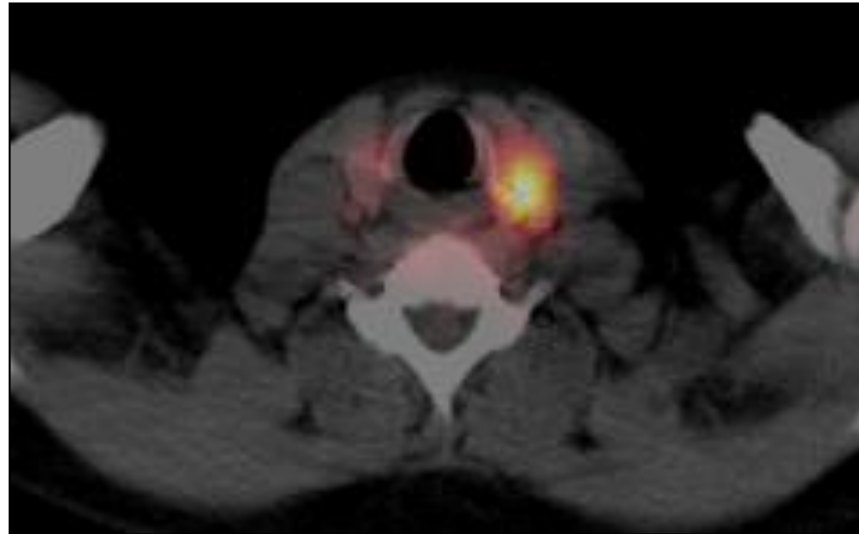
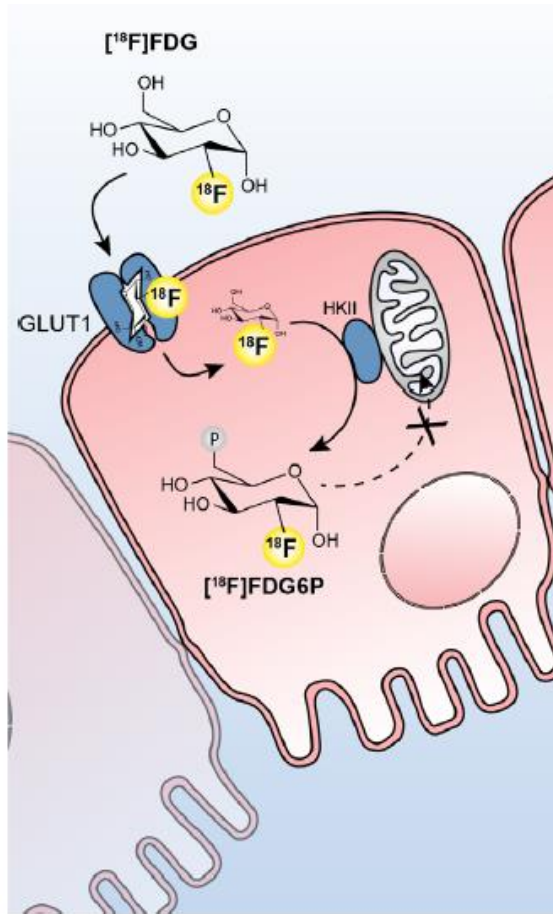
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Thyroid positron-emission tomography

[^{18}F -fluorodeoxyglucose, FDG]

Thyroid PET/CT with ^{18}F FDG



Very high NPV (rule-out test)

PPV not satisfactory

Overlapping SUV_{max}

Efficacy of [^{18}F]FDG PET in Evaluation of Cytological indeterminate Thyroid nodules prior to Surgery (EfFECTS)

Prospective, triple-blinded, randomised controlled multicentre trial performed in 15 hospitals in the Netherlands

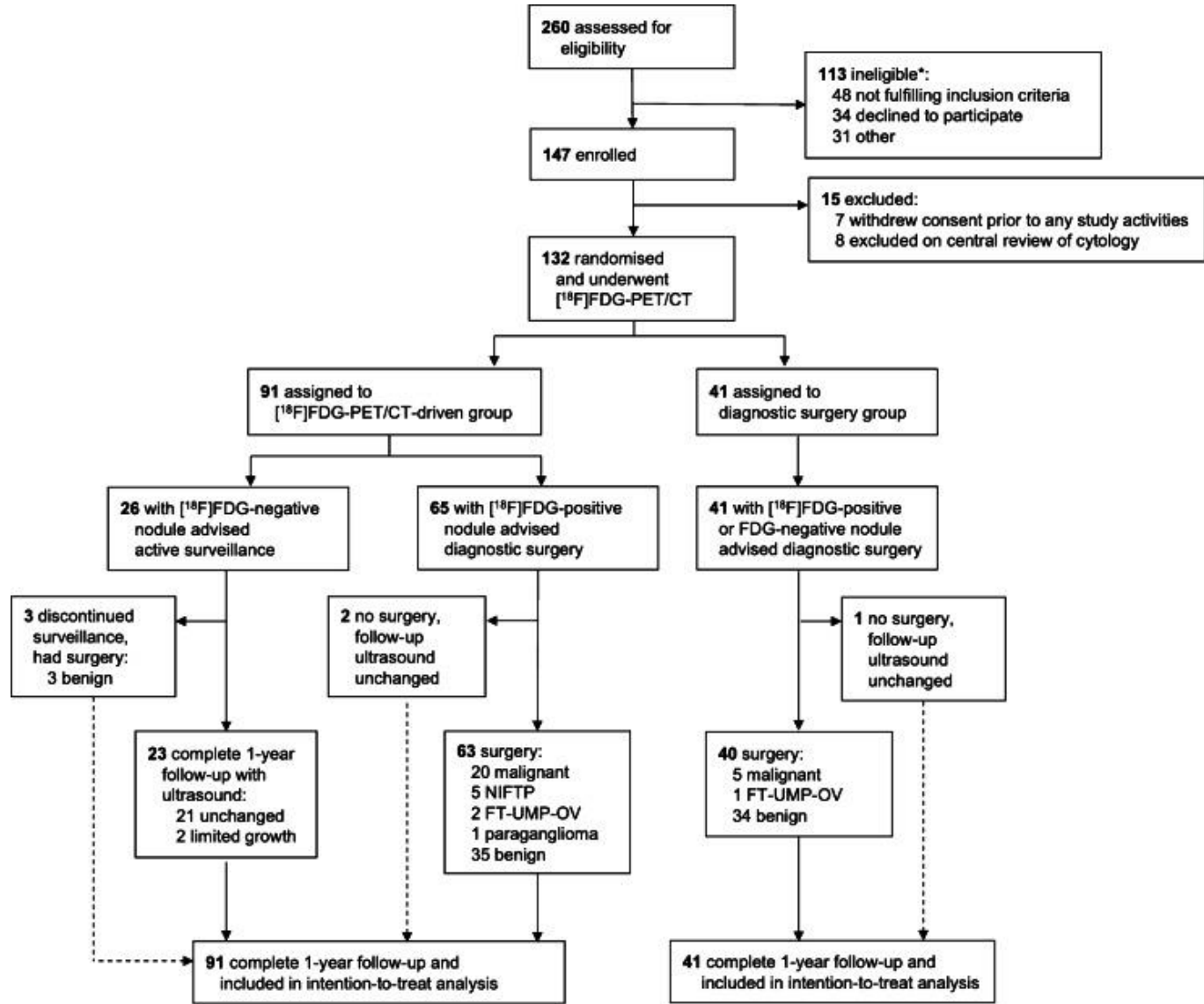
Patients with Bethesda III or IV nodules were randomly assigned to an [^{18}F]FDG-PET/CT-driven group or diagnostic surgery group in a 2:1 ratio

[^{18}F]FDG-PET/CT-driven group

- [^{18}F]FDG-positive nodule scheduled diagnostic surgery.
- [^{18}F]FDG-negative nodule: active surveillance (at least a follow-up US after 1 year).

Diagnostic surgery group

Scheduled surgery, in accordance with current (inter)national guidelines



Patient management

- unbeneficial in 42% of patients in the [^{18}F]FDG-PET/CT-driven group,
- unbeneficial in 83% of patients in the diagnostic surgery group ($p < 0.001$)
- [^{18}F]FDG-PET/CT-driven management avoided 40% diagnostic surgeries for benign nodules. No malignant or borderline tumours were observed in patients under surveillance.

Conclusion

- [^{18}F]FDG-PET/CT changes management, accurately and oncologically safely, reducing futile surgeries by 40%

Radiomics: a perspective

Thyroid PET/CT with ¹⁸FDG: radiomic analysis

Thyroid Incidentalomas

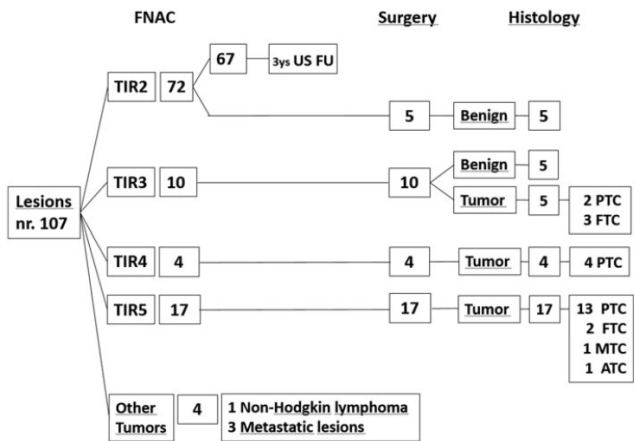


TABLE 2. DISTRIBUTION OF POSITRON EMISSION TOMOGRAPHY FUNCTIONAL PARAMETERS AND NONREDUNDANT RADIOMICS FEATURES IN THE TWO SUBGROUPS OF PATIENTS WITH BENIGN AND MALIGNANT NODULAR DISEASE

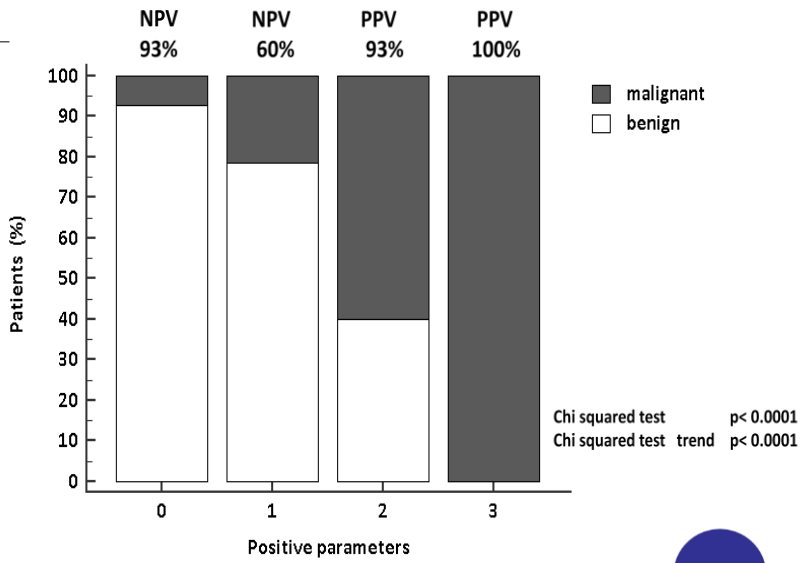
Variable	Benign lesions (n=77)	Malignant lesions (n=30)	p*
PET metrics			
SUVmax	6.71 (4.52–10.96)	10.81 (7.21–14.71)	0.0146
SUVmean	2.79 (2.39–3.57)	3.88 (2.78–5.64)	0.0040
SUVpeak	3.45 (2.98–5.57)	7.11 (4.25–10.90)	0.0005
MTV (mL)	3.64 (2.48–7.22)	10.75 (4.10–29.66)	0.0002
TLG	11.61 (8.73–15.30)	44.69 (19.55–81.28)	<0.0001
AUC-CSH	0.42 (0.40–0.50)	0.44 (0.42–0.50)	0.5930
CV	0.40 (0.29–0.59)	0.54 (0.28–0.65)	0.2580
Radiomics			
Shape_Sphericity	0.67 (0.53–0.78)	0.79 (0.72–0.82)	0.0004
Shape_Maximum2DDiameterSlice	32.20 (23.20–45.30)	22.85 (20.12–29.55)	0.0018
Firstorder_Energy	5592.0 (1533.40–20203.00)	1178 (629.30–3541.40)	0.0005
GLCM_Contrast	150.30 (86.50–265.20)	253.8 (179.10–328.10)	0.0025
GLCM_InverseDifferenceMoment	0.13 (0.11–0.18)	0.09 (0.07–0.13)	0.0003
GLCM_SumSquares	183.20 (142.30–226.10)	212.10 (185.80–239.30)	0.0380

TABLE 4. MULTIVARIATE ANALYSIS (STEPWISE LOGISTIC REGRESSION) RESULTS

Variable	OR [CI]	p	Likelihood ratio test	Hosmer and Lemeshow goodness of fit test	Bootstrap (R=1000) optimism-corrected AUC-ROC
SUVmax	4.15 [1.22–14.19]	0.0231	<0.0001	0.9999	0.830
TLG	4.52 [1.39–14.71]	0.0123			
Shape_Sphericity	18.11 [3.68–89.11]	0.0004			

Results including the five functional PET parameters and six radiomics features that were significant at univariate analysis. AUC-ROC, area under the curve-receiver operator characteristic.

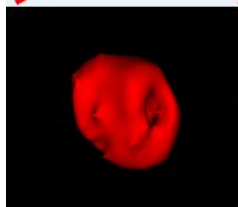
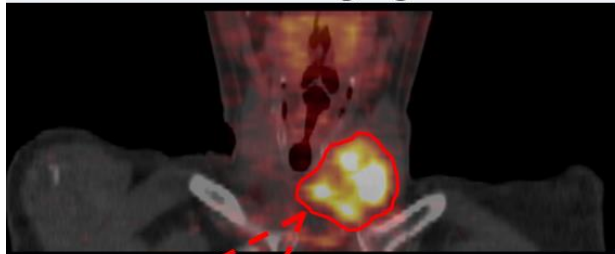
Ceriani et al. Thyroid 2020



Thyroid PET/CT with ^{18}F FDG: radiomic analysis

Bethesda III-IV nodules

^{18}F -FDG PET imaging



3D volume

Radiomics analysis

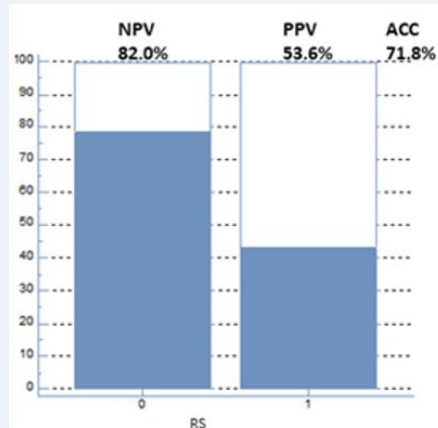
Shape-based features



First-order features



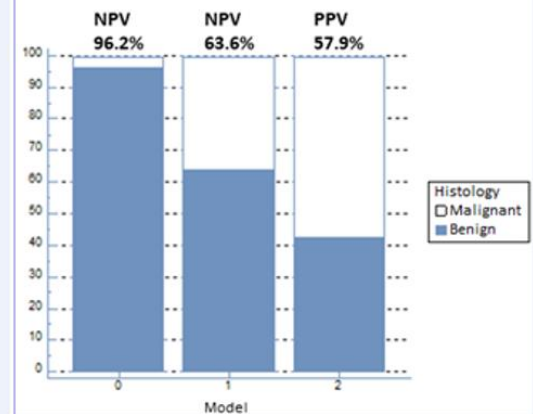
Second-order features



Radiomics signature

Table 2 Selected features from LASSO logistic regression analysis

Feature	Regression coefficient
shape_Sphericity	-0.157
glen_Autocorrelation	-0.285



Radiomics signature
+
Cytology results

Bethesda + PET-radiomics = increased accuracy

Giovannella et al. Endocrine 2021

KEY POINTS

QUESTION: What is the current role of molecular imaging in evaluating thyrotoxicosis and thyroid nodules?

PERTINENT FINDINGS: Thyroid scintigraphy with ^{123}I or $^{99\text{m}}\text{Tc}$ -pertechnetate allows a real-time differentiation of different forms of thyrotoxicosis, the exclusion of autonomously functioning thyroid nodules from inappropriate biopsy, and the detection of ectopic thyroid tissue. The use of either $^{99\text{m}}\text{Tc}$ -methoxyisobutylisonitrile (MIBI) and ^{18}F -FDG may complement the work-up of cytologically indeterminate cold nodules and contribute to reducing the need for diagnostic lobectomies/thyroidectomies.

IMPLICATIONS FOR PATIENT CARE: Thyroid molecular imaging characterizes molecular/functional aspects of different thyroid diseases, even before clinical symptoms become manifest and remains integral to properly managing such conditions.

Giovannella et al. JM; 2021