VRAAG 1: ECHOGRAFISCHE KENMERKEN PALPABELE NODUS

Systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of review quality
Gharib H 2010	• SR (guideline) • Funding/CoI: list provided in article • Search date: not reported • Databases: Medline, Cochrane Library, National Guideline Clearinghouse, AHRQ, CMA, etc. • Study designs: SR, guidelines, primary studies • N included studies: unclear	• Eligibility criteria: patients with palpable nodus	US criteria for FNAB	Diagnosis of malignancy: • Marked hypoechogenicity: Sp 41.4-92.2% • Microcalcifications: Sp 44.2-95.0% • Irregular or microlobulated margin: Sp 48.3-91.8% • Chaotic arrangement or intranodular vascular images: Sp 80% • All features have low Se	Level of evidence: B • Unclear how quality appraisal was done, but use of levels of evidence and grades of recommendation • No results provided for individual studies

Primaire studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
Popli MB 2012	• Diagnostic accuracy study • Funding/CoI: no funding, no CoI declared • Setting: single centre, India • Sample size: N=203 • Duration: inclusion 9/2009-8/2010	• Eligibility criteria: patients with clinically palpable thyroid nodules referred for investigation; no multinodular goiter (N=73); size at least 1 cm; no purely cystic nodule; no inadequate FNAC • *A priori* patient characteristics: females 92%, age 15-62y • Prevalence: 18.3% malignant nodules	Index test: Neck US Reference test: Cytopathology (US-FNAC)	Diagnosis of malignancy: Poorly defined margins: • Se: 84% • Sp: 89% • PPV: 63% • NPV: 96% Calcification: • Se: 86% • Sp: 76% • PPV: 45% • NPV: 96% Microcalcification: • Se: 66% • Sp: 98% • PPV: 88% • NPV: 93% Macrocalcification: • Se: 20% • Sp: 78% • PPV: 17% • NPV: 81% Solid or predominantly solid composition: • Se: 89% • Sp: 54% • PPV: 30% • NPV: 95% Absent or thick irregular halo: • Se: 70% • Sp: 66% • PPV: 32% • NPV: 91% Markedly hypoechoic: • Se: 66% • Sp: 87% • PPV: 54% • NPV: 92% Shape taller than wide: • Se: 77% • Sp: 80%	Level of evidence: B • Unclear if consecutive patients • Blinded image review, unclear if pathology review was blinded • Only per-lesion analysis

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
				• PPV: 47% • NPV: 94%	
Polyzos SA 2009	• Diagnostic accuracy study, retrospective • Funding/CoI: funding not reported, no CoI declared • Setting: single university centre, Greece • Sample size: N=796 • Duration: inclusion 1987-2004	• Eligibility criteria: patients with a palpable solitary thyroid nodule or at least one dominant nodule within a multinodular goiter detected by clinical examination, US or both; at least one US before any medical intervention; at least one thyroid FNAB • *A priori* patient characteristics: females 87%, mean age 48.2y • Prevalence: 8.7% patients with malignant nodules	Index test: Neck US Reference test: FNAB	Diagnosis of malignancy: Solitary nodule: • Se: 57% (28/49) • Sp: 68% (347/509) • PPV: 15% (28/190) • NPV: 94% (347/368) Solid composition: • Se: 58% (23/40) • Sp: 48% (208/435) • PPV: 9% (23/250) • NPV: 92% (17/225) US diameter at least 4.5 cm: • Se: 15% (5/33) • Sp: 95% (390/412) • PPV: 19% (5/27) • NPV: 93% (390/418)	Level of evidence: B • 941 consecutive patients, 796 of which underwent US • Exclusion of patients with indeterminate and non-diagnostic cytology, or benign cytology if followed for less than 1 year; unclear why different number of patients per US-criterion • Blinding not reported
Lin JH 2009	• Diagnostic accuracy study, retrospective • Funding/CoI: not reported • Setting: single university centre, Taiwan • Sample size: N=317 • Duration: inclusion 1/1993-12/2006	• Eligibility criteria: patients with palpable thyroid nodules that underwent thyroid total lobectomy or TT; no locally advanced thyroid nodules or distal metastases, known thyroid disease, radiation therapy to head and neck area • *A priori* patient characteristics: females 74%, mean age 43.5y • Prevalence: 21.4% malignant nodules	Index test: Neck US (real-time ultrasonographic scanner) Reference test: Histopathology	Diagnosis of malignancy: • Se: 52% • Sp: 94% • PPV: 64% • NPV: 90%	Level of evidence: B • Important selection bias by only selecting patients that underwent surgery • 317 out of 378 included patients underwent US • US criteria for malignancy = at least one of the following: solid echo structure, hypoechogenicity, fine calcification, and ill-defined margin
Alexander EK 2004	• Diagnostic accuracy study, retrospective • Funding/CoI: not reported, but 1 author collaborates with Pfizer • Setting: single centre, US • Sample size: N=747 • Duration: inclusion 1995-2000	• Eligibility criteria: patients with at least 1 solid (less than 25% cystic) thyroid nodule evaluated with US-guided FNA • *A priori* patient characteristics: females: benign 89% vs. malignant 86%; mean age: 50 vs. 45y; maximal size: 25 +/- 12 mm vs. 24 +/- 11 mm • Prevalence: 13.9% malignant nodules	Index test: Neck US Reference test: FNA and/or surgical pathology	Diagnosis of malignancy: Solitary nodule: • Se: 46% (48/104) • Sp: 70% (447/643) • PPV: 20% (48/244) • NPV: 89% (447/503)	Level of evidence: B • Selection of patients not clearly reported: selection criteria? Why did they receive US? • Consecutive patients, inclusion based on receiving of reference test • Blinding not reported • No 2x2 tables possible for ratio of longest to shortest axis
Asteria C 2008	• Diagnostic accuracy study, prospective • Funding/CoI: not reported • Setting: single centre, Italy	• Eligibility criteria: patients with thyroid nodules who were referred to the Thyroid Unit of the Department of Endocrinology and Cardiovascular Prevention at the Policlinico MultiMedica; presence	Index test: Neck US: (1) US B-mode and US color-power-Doppler; (2) free-hand real-time US-elastography	Diagnosis of malignancy: Hypoechogenicity: • Se: 65% • Sp: 81% • PPV: 46%	Level of evidence: B • Selection of patients not clearly reported: selection criteria? Why did they receive US? • Consecutive patients

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
	• Sample size: N=67 • Duration: inclusion 1/2006-12/2006	of single or multiple thyroid nodules >10mm; no anatomical abnormalities of the neck (i.e., bull neck) and cystic lesions of completely liquid nature • *A priori* patient characteristics: females 81%, age range 23-83y, mean size 21.3 mm (range 10-50 mm) • Prevalence: 19.8% malignant nodules	<u>Reference test</u>: FNAB or surgical pathology	• NPV: 90% Microcalcification: • Se: 59% • Sp: 84% • PPV: 48% • NPV: 89% Irregular margins: • Se: 76% • Sp: 78% • PPV: 46% • NPV: 93% Absence of halo sign: • Se: 100% • Sp: 14% • PPV: 22% • NPV: 100% Hypoechogenicity + irregular margins: • Se: 65% • Sp: 93% • PPV: 69% • NPV: 91% Hypoechogenicity + microcalcifications: • Se: 41% • Sp: 93% • PPV: 58% • NPV: 86% Irregular margins + microcalcifications: • Se: 53% • Sp: 96% • PPV: 75% • NPV: 89% Hypoechogenicity + irregular margins + microcalcifications: • Se: 41% • Sp: 99% • PPV: 88% • NPV: 87% Elasticity score 3-4: • Se: 94% • Sp: 81% • PPV: 55%	• Blinded US-evaluation, unclear if blinded pathology review • Differential verification • Per-lesion analysis

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
				• NPV: 98%	
Friedrich-Rust 2010	• Diagnostic accuracy study • Funding/CoI: funding not reported; no CoI to declare • Setting: single University centre, Germany • Sample size: N=50 • Duration: inclusion 6/2007-1/2009	• Eligibility criteria: patients presenting for workup of thyroid nodules ≥ 10 mm, non-functioning or hypo-functioning on radionuclide scanning, and FNAB of this nodule performed within the last 3 months or FNAB and/or surgery planned at the time of US examination and finally performed within the study period; no cystic lesions of completely liquid nature, pregnancy, heart failure NYHA III-IV, severe pulmonary hypertension • *A priori* patient characteristics: females 74%, age range 26-79y • Prevalence: 13.2% malignant nodules	Index test: Neck US: (1) conventional US; (2) real-time US-elastography; (3) contrast-enhanced US Reference test: FNAB or surgical pathology	Diagnosis of malignancy: Hypoechogenicity: • Se: 43% • Sp: 59% • PPV: 14% • NPV: 87% Microcalcification: • Se: 43% • Sp: 76% • PPV: 21% • NPV: 90% Absence of halo sign: • Se: 57% • Sp: 39% • PPV: 13% • NPV: 86% Irregular margins: • Se: 57% • Sp: 85% • PPV: 36% • NPV: 93% Oval shape: • Se: 29% • Sp: 65% • PPV: 11% • NPV: 86% Pattern 4 vascularity: • Se: 29% • Sp: 91% • PPV: 33% • NPV: 89% Pattern 3-4 vascularity: • Se: 71% • Sp: 46% • PPV: 17% • NPV: 91% Elasticity score 3-4: • Se: 86% • Sp: 87% • PPV: 50%	Level of evidence: B • Unclear if onsecutive patients • Blinded US-evaluation, unclear if blinded pathology review • Differential verification • Per-lesion analysis

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
				NPV: 98%	
Kwak JY 2011	• Diagnostic accuracy study, retrospective • Funding/CoI: supported by a faculty research grant from Yonsei University College of Medicine; no CoI to declare • Setting: single University centre, Korea • Sample size: N=1638 • Duration: inclusion 5/2008-12/2008	• Eligibility criteria: patients that underwent US-FNAB for nodules of at least 1 cm • *A priori* patient characteristics: mean age 50.6y, mean size 19.9 mm (range 10-80 mm) • Prevalence: 16.6% malignant nodules	Index test: Neck US Reference test: FNAB or surgical pathology	Diagnosis of malignancy: Solid composition: • Se: 93% • Sp: 42% • PPV: 24% • NPV: 97% (Marked) hypoechogenicity: • Se: 84% • Sp: 62% • PPV: 31% • NPV: 95% Irregular margins: • Se: 33% • Sp: 99% • PPV: 86% • NPV: 88% Microcalcification: • Se: 40% • Sp: 96% • PPV: 69% • NPV: 89% Taller than wide shape: • Se: 51% • Sp: 96% • PPV: 71% • NPV: 91%	Level of evidence: B • Consecutive patients • Blinding not clearly reported • Differential verification • Per-lesion analysis
Tamsel S 2007	• Diagnostic accuracy study, prospective • Funding/CoI: not reported • Setting: single University centre, Turkey • Sample size: N=134 • Duration: inclusion 6/2005-12/2005	• Eligibility criteria: not clearly reported • *A priori* patient characteristics: females 80%, mean age 48y, mean size 19.1 mm (range 10-60 mm) • Prevalence: 6% malignant nodules	Index test: Neck power Doppler US Reference test: FNAB or surgical pathology	Diagnosis of malignancy: Intranodular vascularity: • Se: 100% • Sp: 11% • PPV: 6% • NPV: 100%	Level of evidence: B • Unclear if consecutive patients, inclusion criteria not reported • Blinded evaluation of imaging and pathology • Per-lesion analysis
Yoon JH 2011	• Diagnostic accuracy study, retrospective • Funding/CoI: funding not reported; no CoI to declare • Setting: single University centre, Korea	• Eligibility criteria: patients that underwent US-FNAB for initial diagnosis of thyroid nodules 3 cm or larger in the longest diameter on US • *A priori* patient characteristics: females 82%, mean age 48y,	Index test: Neck US Reference test: FNAB + findings on follow-up US, or surgical pathology	Diagnosis of malignancy: Solid composition: • Se: 12% • Sp: 96% • PPV: 26% • NPV: 90%	Level of evidence: B • Unclear if consecutive patients • Blinded US-evaluation, unclear if blinded pathology review • Incorporation bias • Differential verification

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Critical appraisal of study quality
	• Sample size: N=661 • Duration: inclusion 2/2002-12/2006	mean size 39 mm (range 30-150 mm) • Prevalence: 11.2% malignant nodules		(Marked) hypoechogenicity: • Se: 76% • Sp: 70% • PPV: 24% • NPV: 96% Ill-defined margin: • Se: 15% • Sp: 100% • PPV: 92% • NPV: 90% Microcalcification: • Se: 19% • Sp: 99% • PPV: 70% • NPV: 91% Non-parallel shape: • Se: 4% • Sp: 100% • PPV: 60% • NPV: 89%	• Per-lesion analysis

Abbreviations: AHRQ: Agency for Healthcare Research and Quality; CMA: …; CoI: conflict of interest; FNAB: fine-needle aspiration biopsy; FNAC: fine-needle aspiration cytology; NPV: negative predictive value; PPV: positive predictive value; Se: sensitivity; Sp: specificity; SR: systematic review; TT: total thyroidectomy; US: ultrasonography.

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