Primo Congresso Interregionale AME Sud - Italia

Associazione Medici Endocrinologi

Primo Congresso Interregionale ANIED Sud - Italia

Responsabile Scientifico Vincenzo Triggiani

Matera, 9-10 Maggio 2014 - HILTON GARDEN INN

5ª SESSIONE: TIROIDE (II PARTE)
(In parallelo alla sessione Dietisti)

L'elastografia: quale utilità nella pratica clinica?

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LA DIAGNOSI DI CARCINOMA TIROIDEO

CLINICA → ECOGRAFIA

FNAC
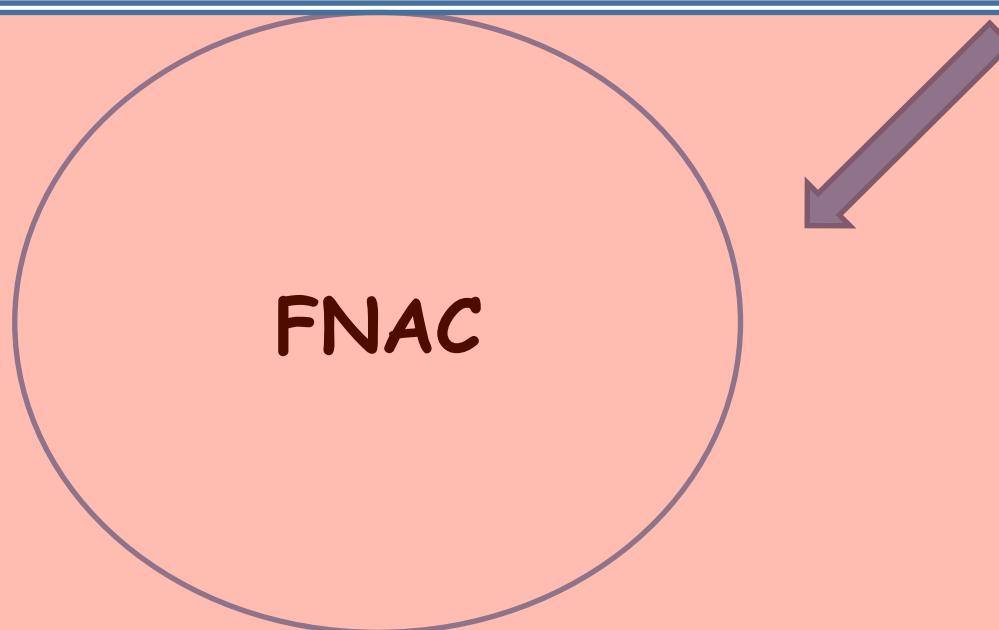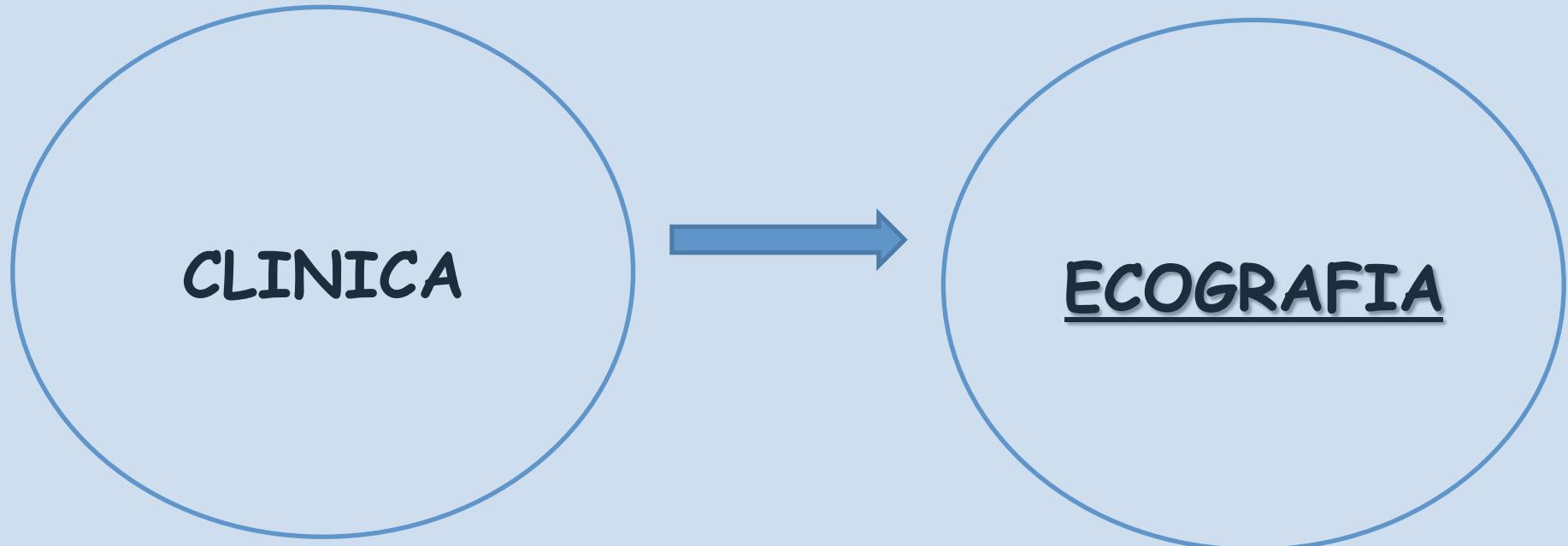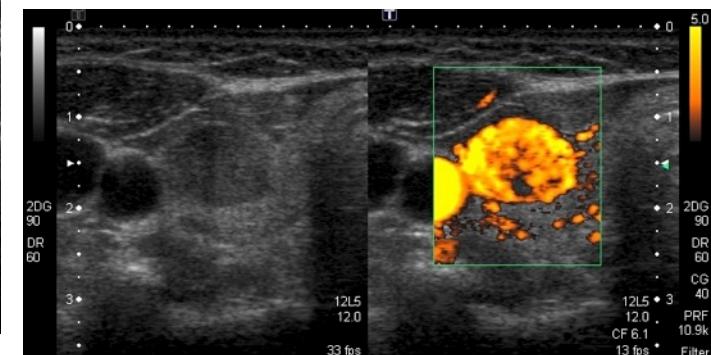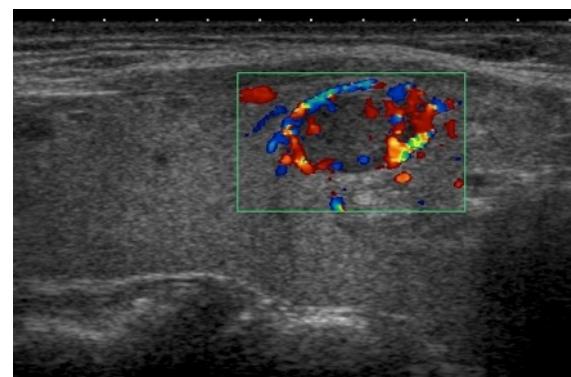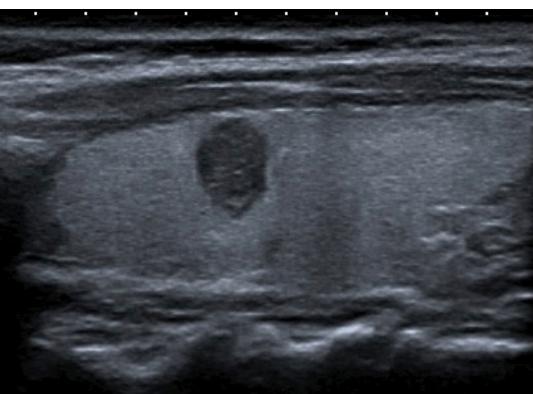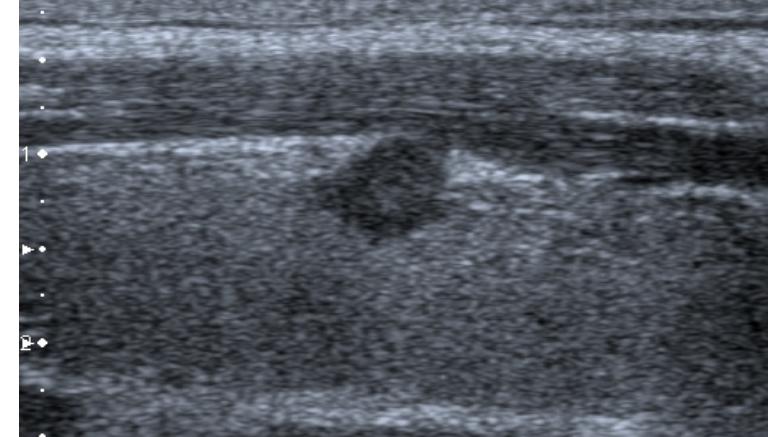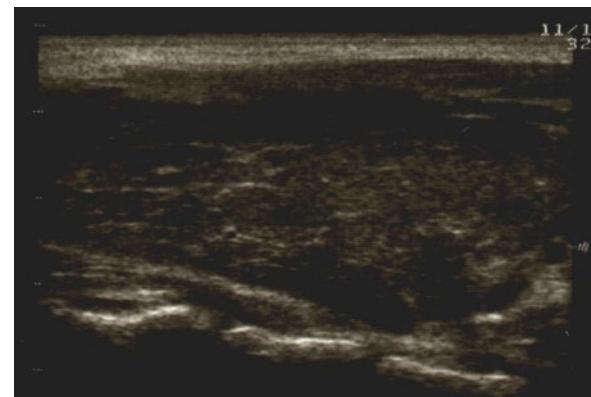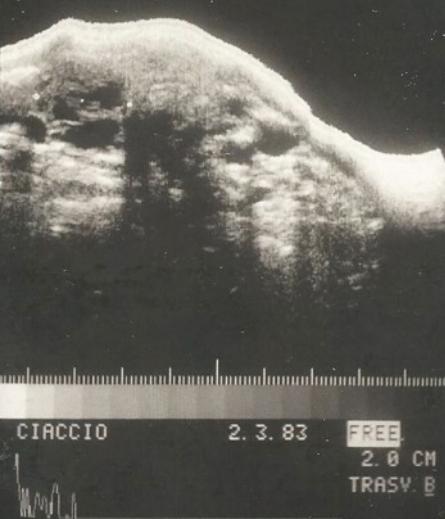
......verso la caratterizzazione tissutale.
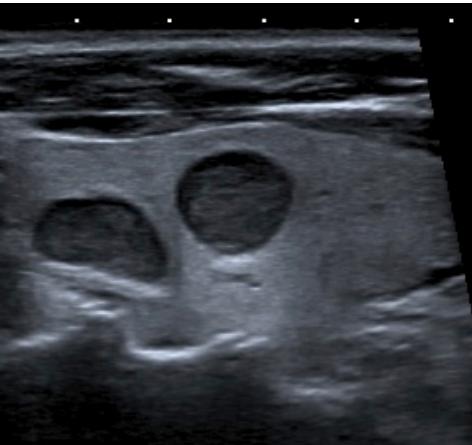
Stiamo chiedendo troppo?
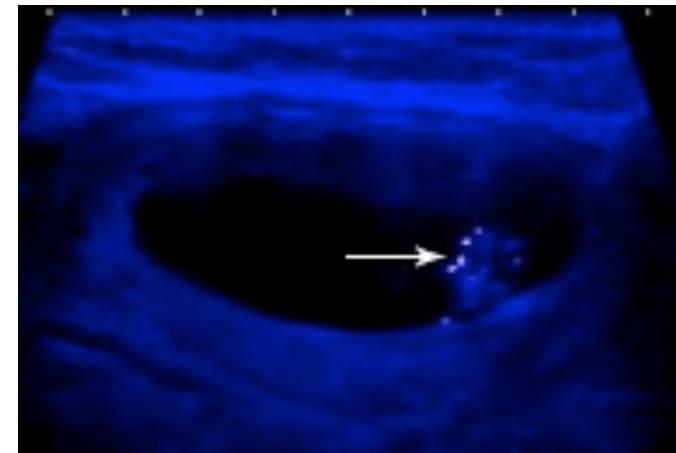
ECOGRAFIA e TUMORI TIROIDEI

- Individuazione e "caratterizzazione" dei noduli … con l'obiettivo di selezionare la/e lesione/i sospetta/e.

- Valutazione dei rapporti tra tiroide ed organi limitrofi; studio stazioni linfonodali.

- Assistenza all' agoaspirato per esame citologico.

IL PROBLEMA
PREVALENZA DEI NODULI E DEL CARCINOMA TIROIDEO

- Compito dell'Ecografista non è la minuziosa descrizione di tutte le lesioni focali intratiroidee ma l'individuazione di quelle sospette.

- Stante la frequenza della patologia nodulare vi è necessità di sviluppare una efficace strategia "cost-effective" per diagnosi e trattamento.

Thyroid incidentaloma. Overdiagnosis and overtreatment of healthy persons with thyroid illness? Dralle H. – Chirurg. 2007 Aug; 78(8): 677-86

[A1] THYROID NODULE GUIDELINES

...attempts to diagnose and treat all small thyroid cancers in an effort to prevent these rare outcomes would likely cause more harm than good.

TABLE 3. SONOGRAPHIC AND CLINICAL FEATURES OF THYROID NODULES AND RECOMMENDATIONS FOR FNA

Nodule sonographic or clinical features	Recommended nodule threshold size for FNA
High-risk history[a]	
Nodule WITH suspicious sonographic features[b]	>5 mm Recommendation A
Nodule WITHOUT suspicious sonographic features[b]	>5 mm Recommendation I
Abnormal cervical lymph nodes	All[c] Recommendation A
Microcalcifications present in nodule	≥1 cm Recommendation B
Solid nodule	
AND hypoechoic	>1 cm Recommendation B
AND iso- or hyperechoic	≥1–1.5 cm Recommendation C
Mixed cystic–solid nodule	
WITH any suspicious ultrasound features[b]	≥1.5–2.0 cm Recommendation B
WITHOUT suspicious ultrasound features	≥2.0 cm Recommendation C
Spongiform nodule	≥2.0 cm[d] Recommendation C
Purely cystic nodule	FNA not indicated[e] Recommendation E

[a]High-risk history: History of thyroid cancer in one or more first degree relatives; history of external beam radiation as a child; exposure to ionizing radiation in childhood or adolescence; prior hemithyroidectomy with discovery of thyroid cancer, [18]FDG avidity on PET scanning; MEN2/FMTC-associated RET protooncogene mutation, calcitonin >100 pg/mL. MEN, multiple endocrine neoplasia; FMTC, familial medullary thyroid cancer.
[b]Suspicious features: microcalcifications; hypoechoic; increased nodular vascularity; infiltrative margins; taller than wide on transverse view.
[c]FNA cytology may be obtained from the abnormal lymph node in lieu of the thyroid nodule.
[d]Sonographic monitoring without biopsy may be an acceptable alternative (see text) (48).
[e]Unless indicated as therapeutic modality (see text).

American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association medical guidelines for clinical practice for the diagnosis and management of thyroid nodules

H. Gharib, E. Papini, R. Paschke, D.S. Duick, R. Valcavi, L. Hegedüs, and P. Vitti; for the AACE/AME/ETA Task Force on Thyroid Nodules*
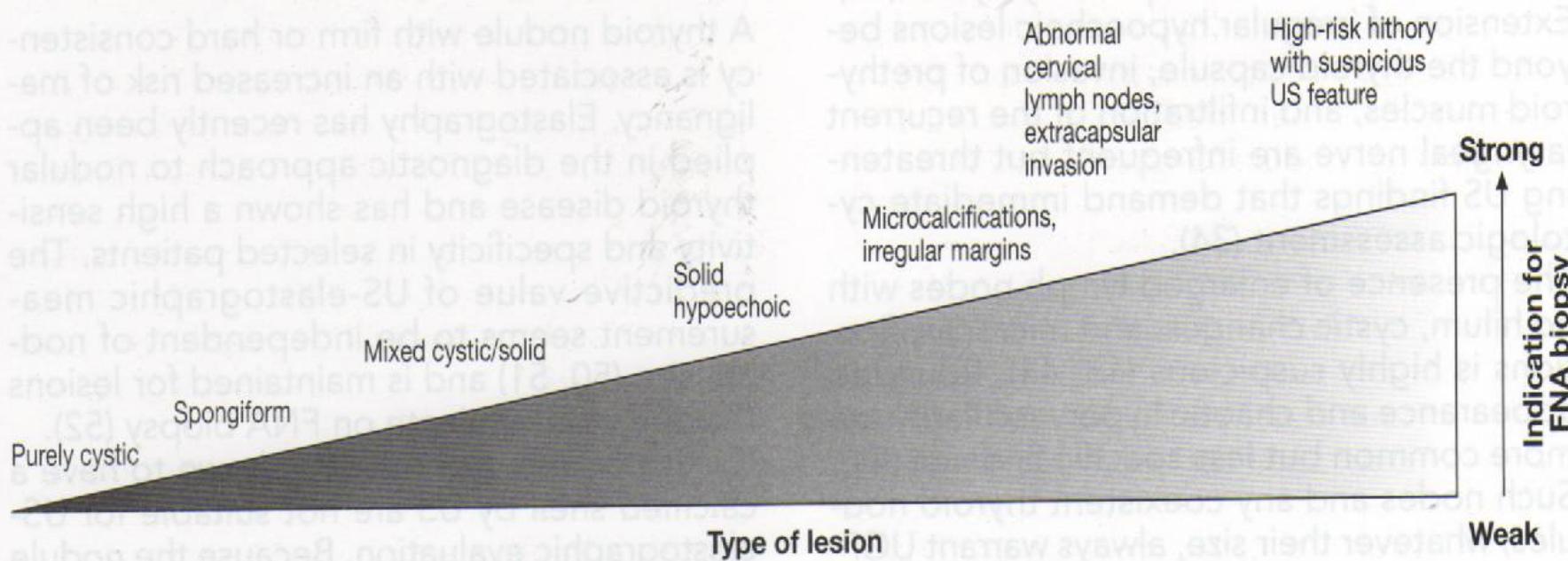

Fig. 2 - Strength of indication for fine-needle aspiration (FNA) biopsy of thyroid nodules on the basis of ultrasonography (US) findings.

- Margini indistinti
- Forma (more tall than wide)
- Vascolarizzazione intralesionale e caotica
- Ipoecogenicità
- Microcalcificazioni
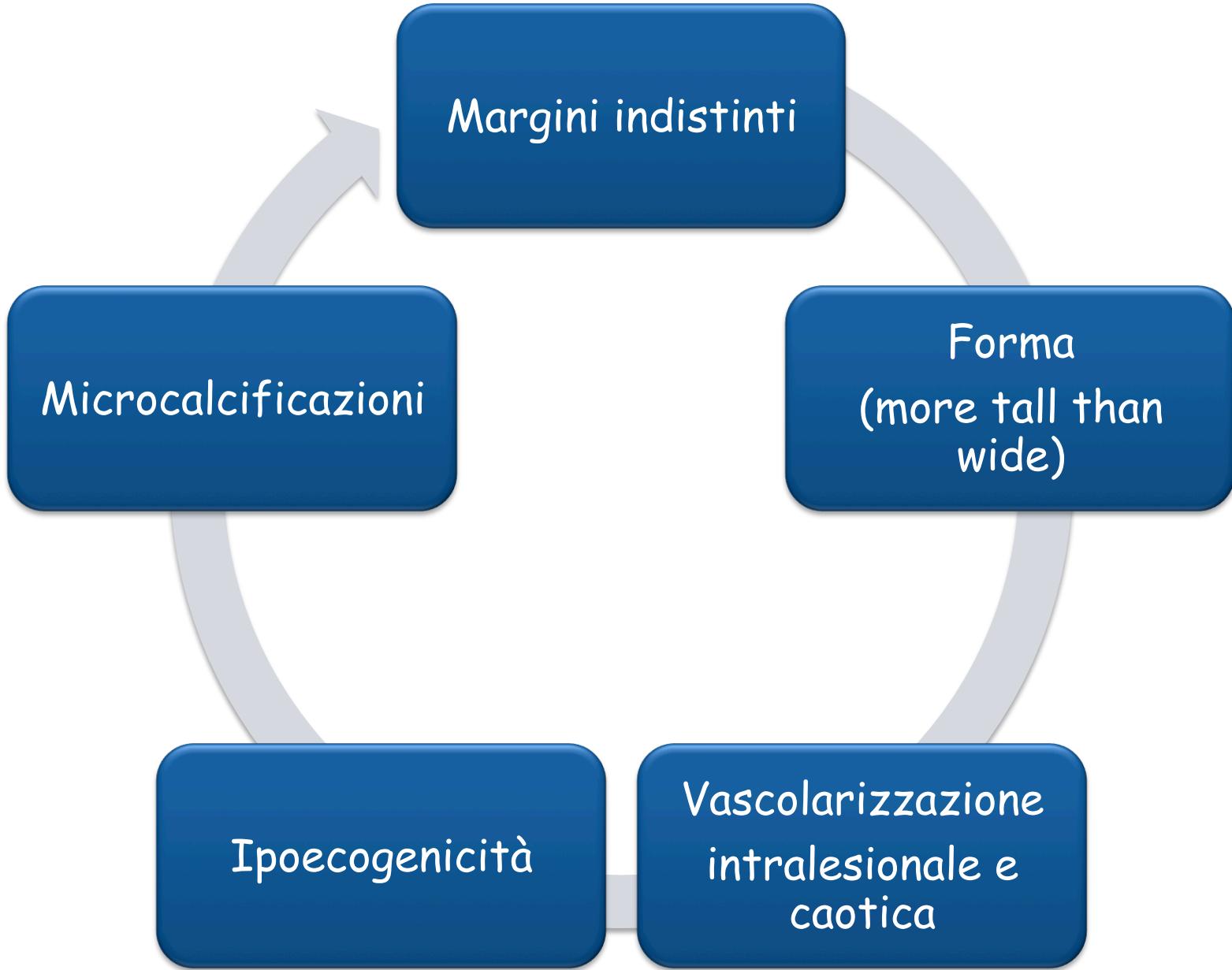
3.4. US elastography

A thyroid nodule with firm or hard consistency is associated with an increased risk of malignancy. Elastography has recently been applied in the diagnostic approach to nodular thyroid disease and has shown a high sensitivity and specificity in selected patients. The predictive value of US-elastographic measurement seems to be independent of nodule size (50, 51) and is maintained for lesions that are indeterminate on FNA biopsy (52).

3.7.4. Novel US techniques

- Elastography and US contrast media currently are not used routinely in the evaluation of thyroid nodules (Grade C; BEL 3)

Elastography is an emerging and promising sonographic technique that requires additional validation with prospective studies (53).

High diagnostic accuracy and interobserver reliability of real-time elastography in the evaluation of thyroid nodules.

Ragazzoni F, Deandrea M, Mormile A, Ramunni MJ, Garino F, Magliona G, Motta M, Torchio B, Garberoglio R, Limone P.

Simple to use, with good interobserver agreement, elastography has all the requisites to become an important complement of conventional US examination in the near future.
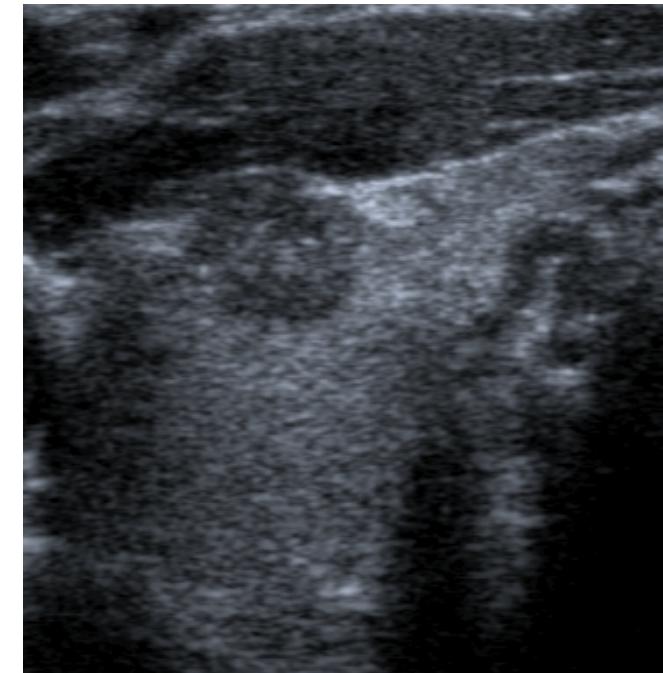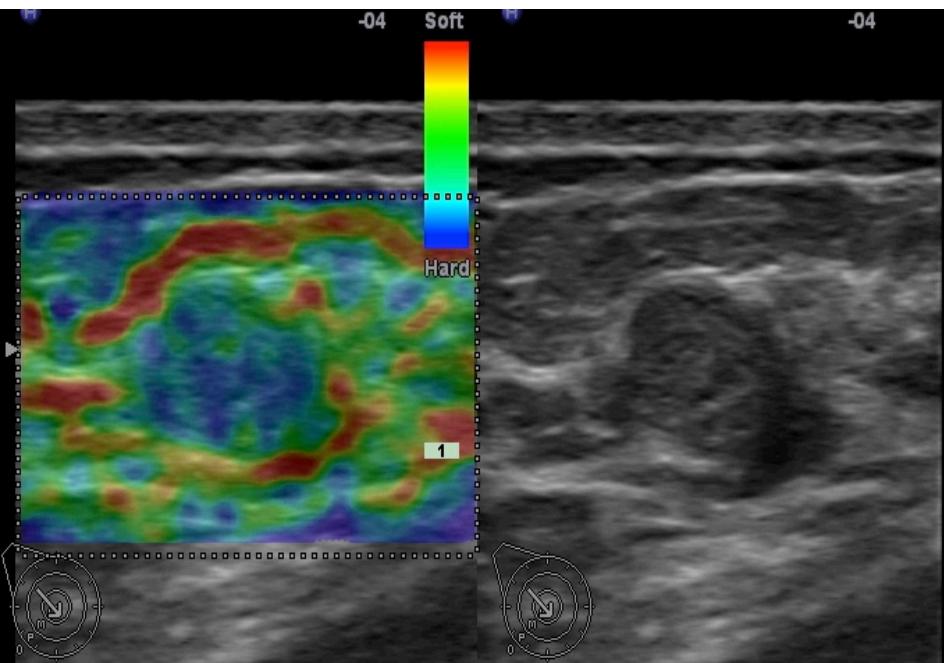
Ultrasound Sensitivity for Thyroid Malignancy Is Increased by Real-Time Elastography: A Prospective Multicenter Study.

Trimboli P, Guglielmi R, Monti S, Misischi I, Graziano F, Nasrollah N, Amendola S, Morgante SN, Deiana MG, Valabrega S, Toscano V, Papini E.

Conclusions:RTE is a valuable tool for detecting malignant **thyroid** lesions with a sensitivity similar to traditional US and CFD features. By adding RTE evaluation, the sensitivity for malignancy of US findings is markedly increased and the selection of nodules that do not need cytology is made more reliable.
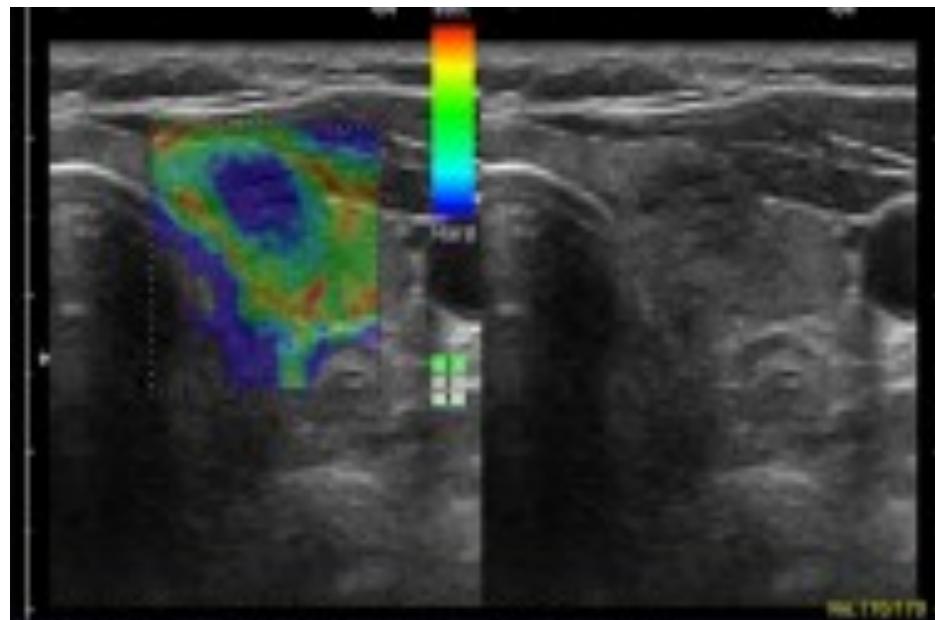
Performance of Elastography for the Evaluation of Thyroid Nodules: A Prospective Study.

Azizi G, Keller J, Lewis Pa M, Puett DW, Rivenbark K, Malchoff CD.

Conclusions: We conclude that TN stiffness measured by **elastography** is an independent predictor of TC with a positive predictive value that is equal to or greater than that of conventional ultrasonographic characteristics. NPV was greater than any other predictor of malignancy.
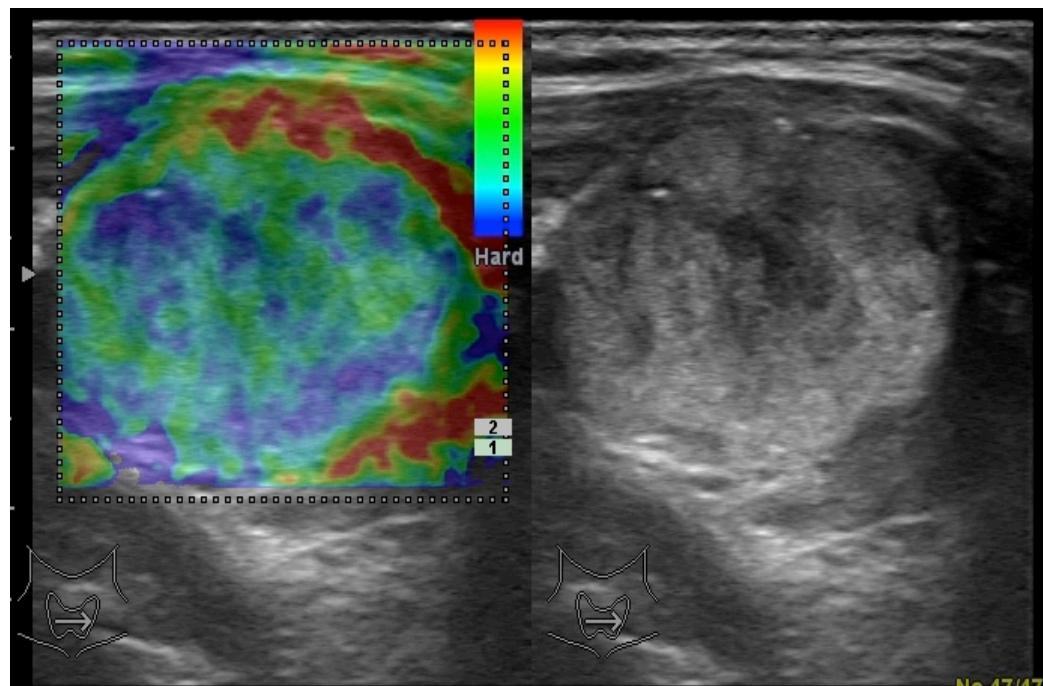
2015 Jan 5.

Shear Wave Elastography in Evaluation of Cervical Lymph Node Metastasis of Papillary Thyroid Carcinoma: Elasticity Index as a Prognostic Implication.

Jung WS[1], Kim JA, Son EJ, Youk JH, Park CS.

Combined use of SWE and BUS was adjunctive to the diagnostic performance of BUS for the prediction of LN metastasis of PTC, and quantitative SWE could predict pathologic prognostic factors of LN metastasis of PTC.

2014 Jan;62(1):67-74.

[Thyroid ultrasonography--considerations and progress in routine diagnostic examinations].

Yamamoto H, Kitaoka M.

Tissue elastography may be useful for the differentiation of follicular adenomas from follicular carcinomas, which is still one of the most difficult clinical challenges for all endocrinologists. It also provides detailed information on the efficacy of thyroid interventions.

2014 Apr;33(4):585-95. doi: 10.7863/ultra.33.4.585.

Virtual touch tissue imaging on acoustic radiation force impulse elastography: a new technique for differential diagnosis between benign and malignant thyroid nodules.

Zhang YF[1], He Y, Xu HX, Xu XH, Liu C, Guo LH, Liu LN, Xu JM.

Virtual Touch tissue elasticity imaging has great potential as an adjunctive tool combined with conventional sonography for differential diagnosis between benign and malignant thyroid nodules.

2014 Mar;33(3):495-502. doi: 10.7863/ultra.33.3.495.

Real-time ultrasound elastography for differentiation of benign and malignant thyroid nodules: a meta-analysis.

Sun J[1], Cai J, Wang X.

These results confirmed those obtained in the previous meta-analysis. Ultrasound elastography has high sensitivity and specificity for identification of thyroid nodules. It is a promising tool for reducing unnecessary fine-needle-aspiration biopsy.

2013 Dec;98(12):4790-7. doi: 10.1210/jc.2013-2672. Epub 2013 Sep 24.

Comparison of elastographic strain index and thyroid fine-needle aspiration cytology in 631 thyroid nodules.

Magri F[1], Chytiris S, Capelli V, Gaiti M, Zerbini F, Carrara R, Malovini A, Rotondi M, Bellazzi R, Chiovato L.

The elastographic SI has a high sensitivity, specificity, and negative predictive value for the diagnosis of thyroid malignancy both in the presence and in the absence of ATD. If our data on USE are also confirmed in THY3 nodules, FNAC could be avoided in a number of thyroid nodules with certain features.
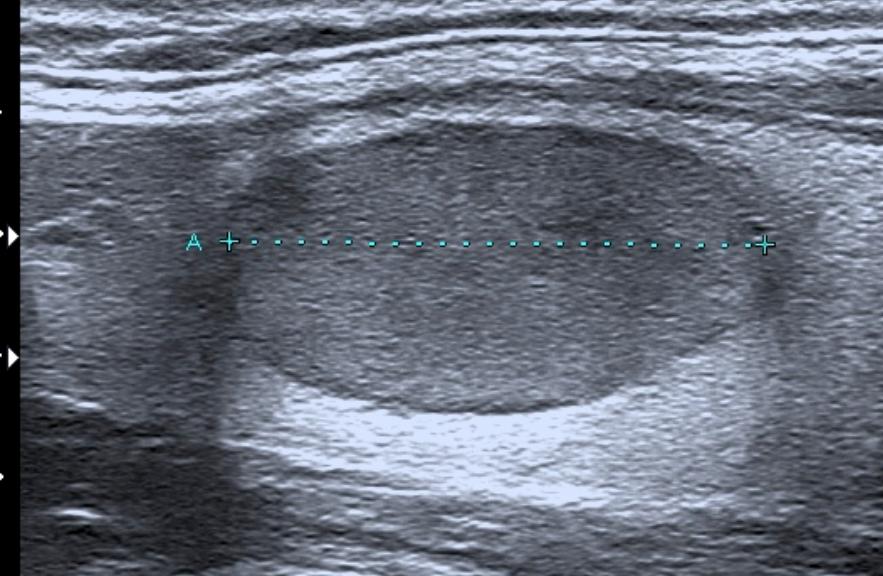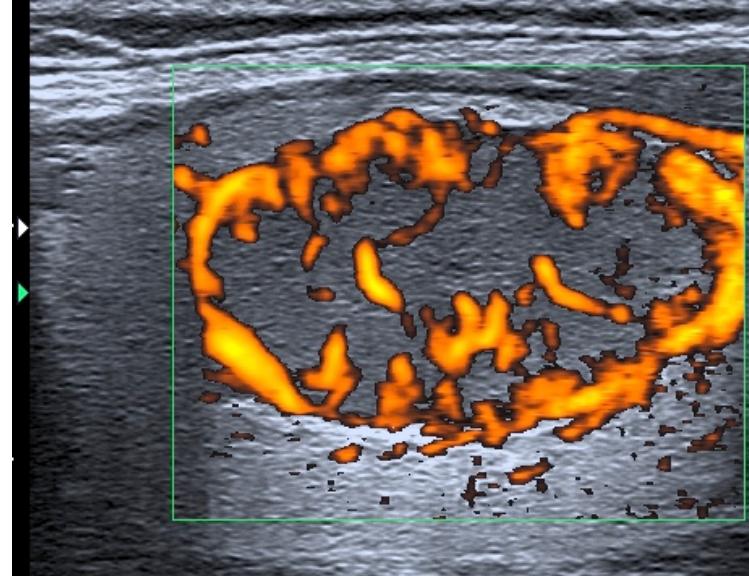
Not everybody agrees
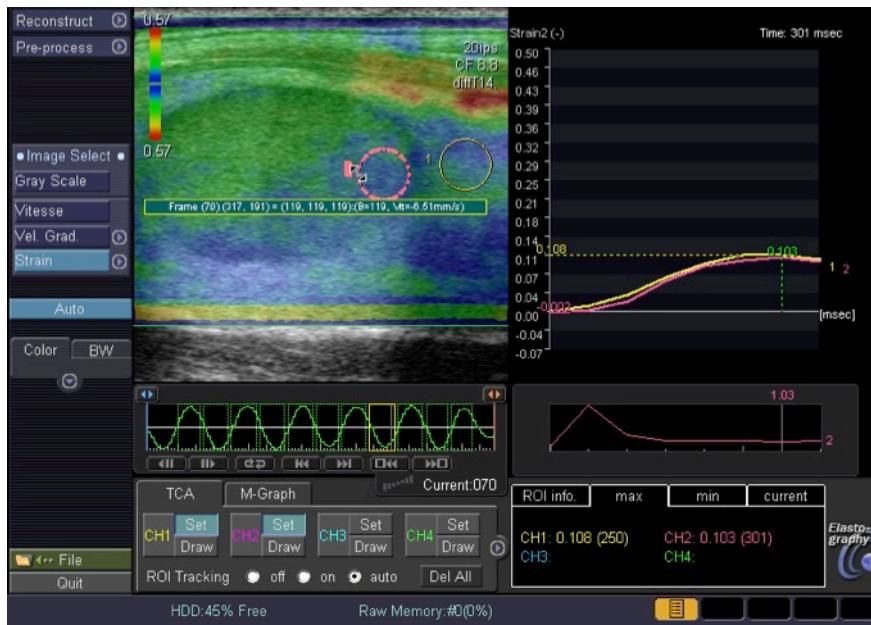
Diagnostic performance of gray-scale US and elastography in solid thyroid nodules

Retrospective study on 703 nodules in 676 patients
Mechanical compression elastography comparing Rago's and Asteria's classifications with gray-scale alone and in combination

……**Elastography alone and the combination of elastography and gray-scale had inferior diagnostic value compared to gray-scale US alone.**

Ultrasound-Elastography is not superior to gray-scale ultrasound in predicting malignancy in thyroid nodules

Ünlütürk U. et al. Thyroid 2012, 22(10); p 1031-38

- Prospective study on 237 nodules in 194 patients in two years
- 3-point scale RTE and strain ratio
- Sensitivity, specificity, PPV, NPV and accuracy of RTE were 47%, 80%, 44%, 83% et 72%, respectively

……… **US Elastography had a limited sensitivity and positive predictive value in detecting malignant thyroid nodules and was not superior to gray-scale and color doppler US.**

L'elastosonografia è una tecnica di imaging che fornisce informazioni relative alla elasticità dei tessuti e che viene utilizzata nella pratica clinica basandosi sul presupposto che alcuni processi patologici, come il cancro, inducono modificazioni della caratteristiche fisiche dei tessuti ammalati.

L'elastografia può essere considerata una sorta di "**palpazione elettronica**". I tumori maligni sono fino a dieci volte più rigidi ed incompressibili dei tessuti circostanti.

SCORE ELASTOSONOGRAFICO

SCORE 1:
Presenza di aspetto di trittratificazione cromatica (blu-verde-rossa)

Riscontro prevalente nelle forme liquide

SCORE 2:
Prevalenza di verde con qualche eventuale punto blu, incostante per sede

SCORE 3:
Prevalentemente verde ma contenente qualche macchia blu

PREVALENTEMENTE ELASTICO:
riscontro prevalente nelle forme benigne

SCORE 4:
Quasi completamente blu con qualche eventuale punto verde preferibilmente alla periferia

SCORE 5:
Completamente blu a cui si associa un alone blu periferico al nodulo

PREVALENTEMENTE RIGIDO:
riscontro prevalente nelle forme maligne

L'immagine elastografica è espressa con una scala cromatica nel quale al rosso corrispondono i tessuti elastici, al blu i tessuti anelastici, al verde i gradi intermedi di elasticità.
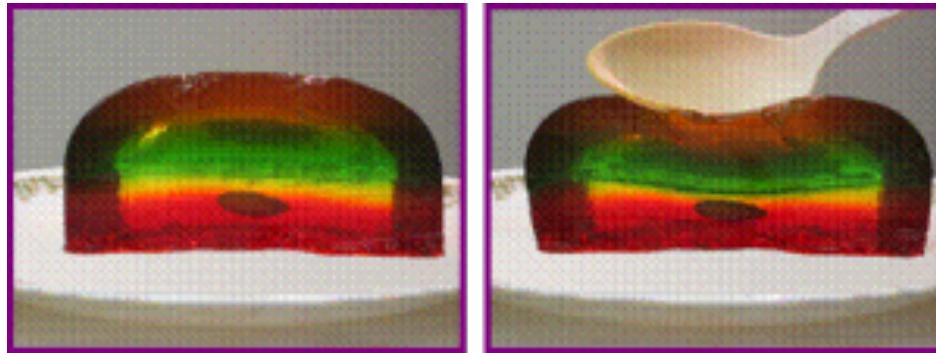
Il principio di base dell'elastografia risiede nel fatto che la compressione del tessuto esaminato con la sonda dell'ecografo produce una **deformazione**, valutata come variazione della distanza tra due punti, differente a seconda del suo grado di "**comprimibilità**", minore nei tessuti duri e maggiore nei tessuti soffici, che può essere rilevata e quantificata attraverso software dedicati.
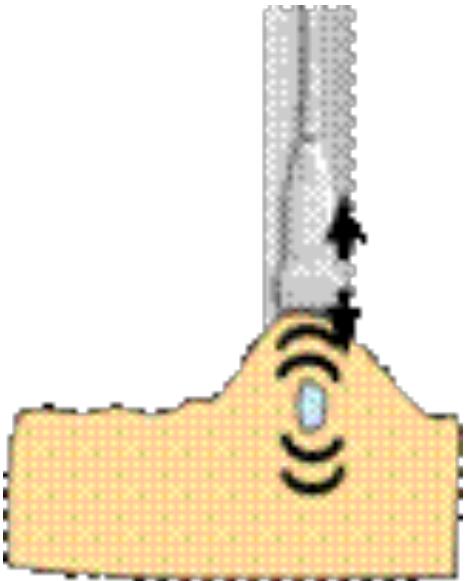
Elastosonografia a mano libera si avvale della compressione manuale ottenuta imprimendo con il trasduttore leggere compressioni manuali ritmiche sull'organo esaminato. L'esame permette la visualizzazione dell'elastogramma sotto forma di un'immagine sovrapposta a quella in B-mode ed utilizza il confronto dei dati in RF tra l'immagine prima della compressione e quella ottenuta durante compressione per fornire una valutazione della elasticità del tessuto.

Elastosonografia con compressione meccanica ottenuta mediante l'emissione di impulsi a maggiore energia e a bassa frequenza (transient elastography), con valutazione della deformazione ottenuta dalla pressione acustica (strain). Questo sistema è costituito da un tradizionale ecografo affiancato da un sistema di elaborazione delle immagini e da un dispositivo che consente la rappresentazione dei risultati dell'elaborazione (modulo elastografico).

In questo caso la sonda ecografica oltre a permettere di ottenere le immagini tradizionali in B-mode in scala di grigio viene utilizzata anche per produrre uno stimolo meccanico sul tessuto e la risposta a questo stimolo da parte del tessuto in esame sarà rappresenta in scala cromatica di "durezza" e mediante valori numerici.
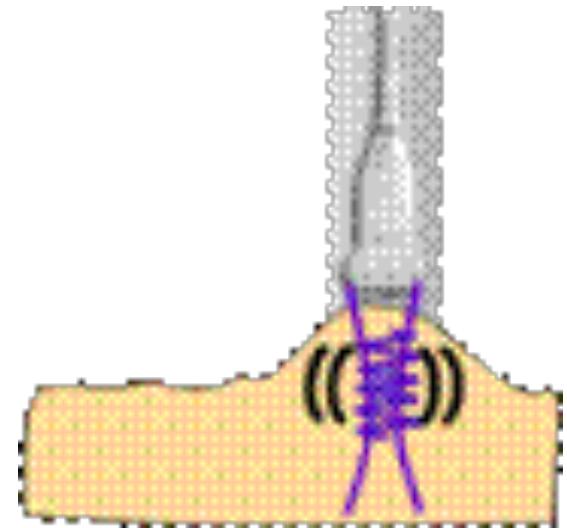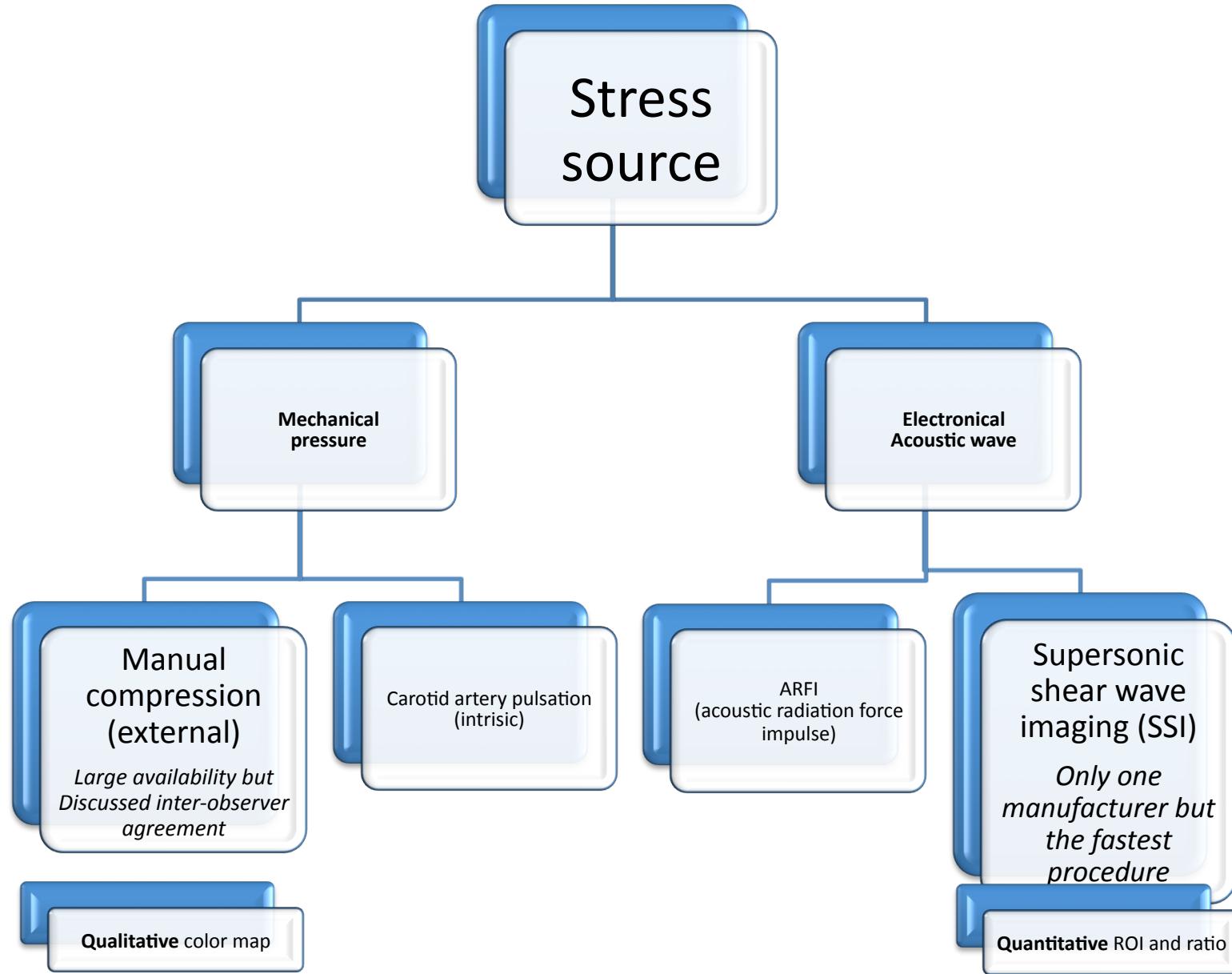
Manual compression - measurement of tissue displacement (the strain)

STATIC ELASTOGRAPHY

Compression Force

Soft Mass | Hard Mass

E

Strain for Soft Mass
A >> B

Strain for Hard Mass
A ≈ B

compression | Displacement | Strain

soft

hard

soft

spatial differential

soft ⟶ large strain

hard ⟶ small strain
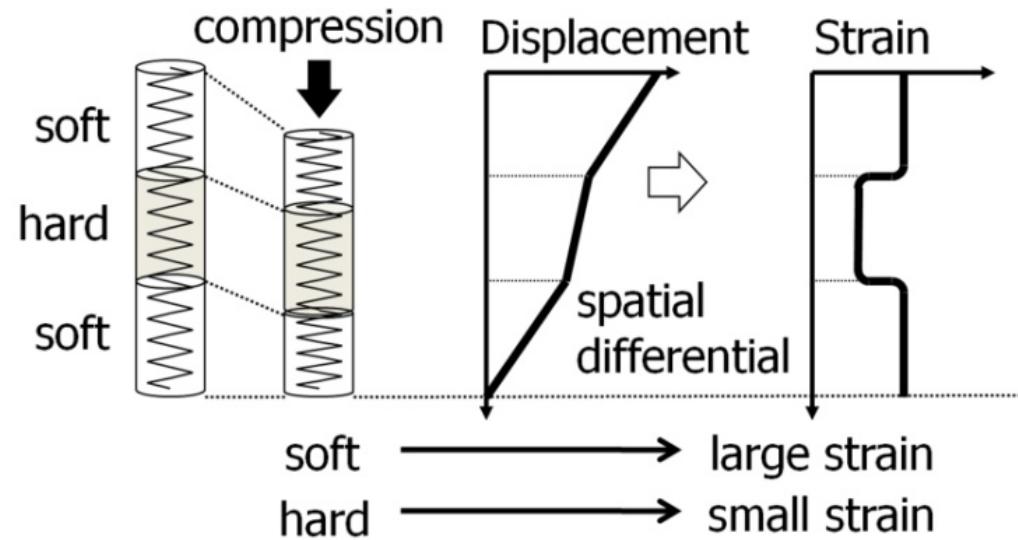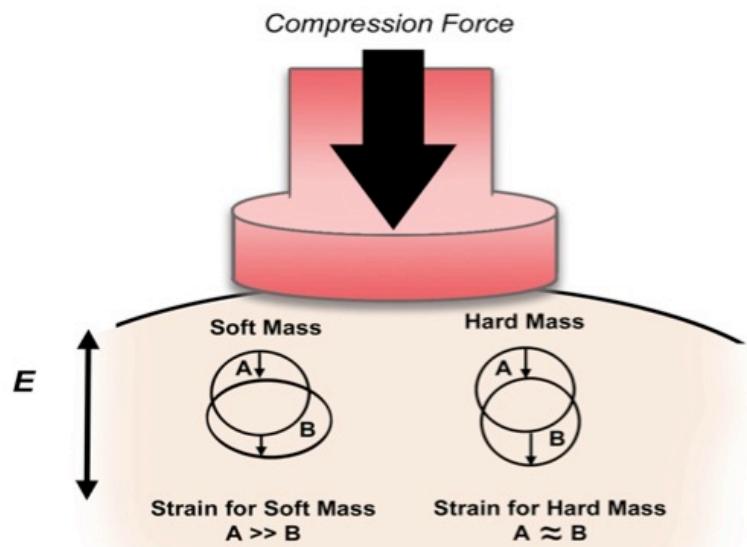
Tissue displacement (strain) may be measured by tracking longitudinal movement of tissue before and after compression.

Strain is greater in soft tissue compared to hard tissue, because soft tissue will easily deform when subjected to external pressure.

Strain elastography provides <u>qualitative information</u>. Young's modulus cannot be directly calculated. However, <u>strain ratios </u>may be calculated by comparing the strain of a lesion to the surrounding normal tissue.

Manual compression elastography
also called **Real Time Elastography (RTE)**

Light manual compression
Longitudinal plane
At least 3 cycles
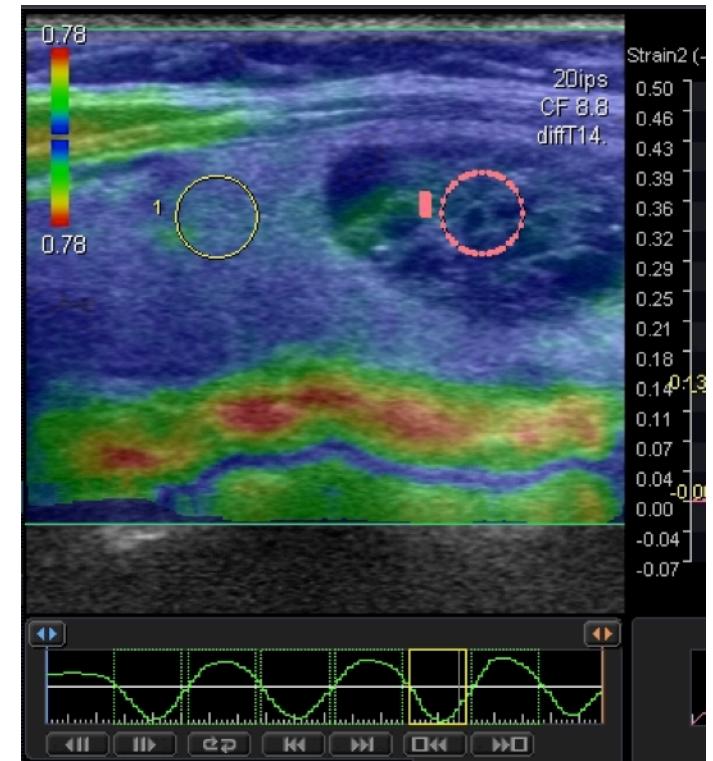
Quality control
Check the cycle for amplitude and regularity

Qualitative color map : manual pressure RTE

interpret the color map: the Rago classification

PROBABLY BENIGN

SUSPICIOUS

Figure 2

a. b. c. d. e.
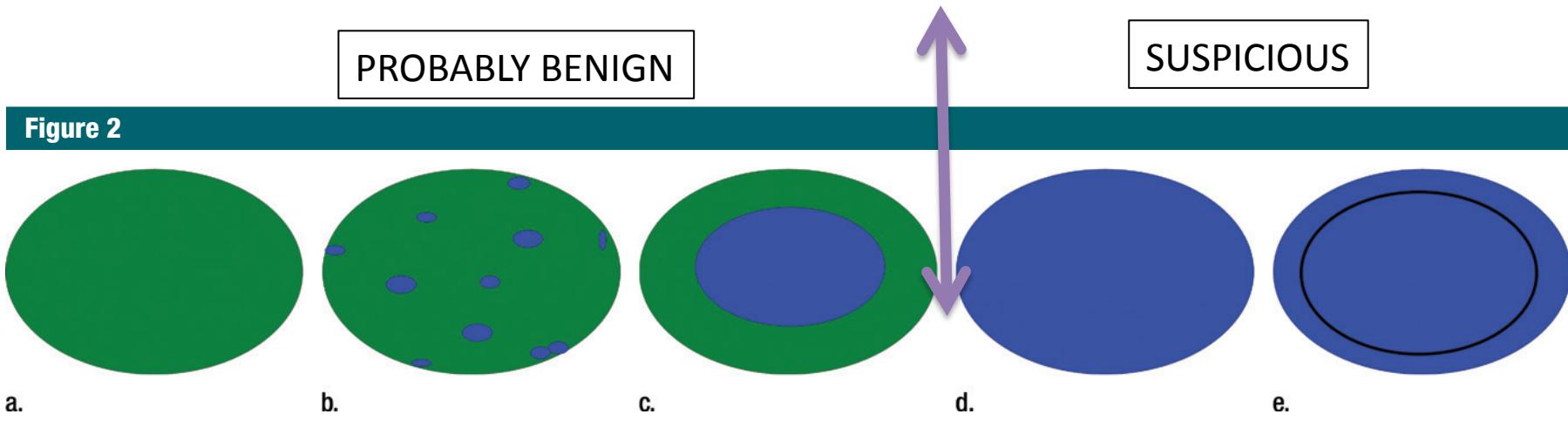
Figure 2: Elastography scores according to Rago criteria. **(a)** A score of 1 indicated even elasticity in the whole nodule. **(b)** A score of 2 indicated elasticity in a large part of the nodule. **(c)** A score of 3 indicated elasticity only at the peripheral part of the nodule. **(d)** A score of 4 indicated no elasticity in the nodule. **(e)** A score of 5 indicated no elasticity in the nodule or in the area showing posterior shadowing.

RAGO T. et al. Elastography: New Developments in Ultrasound for Predicting Malignancy in Thyroid Nodules JCEM 2007, 92(8): 2917-2922

Diagnostic value for manual pressure (RTE)

Study	Method	Nodules number	Carcinomas (%)	Sensitivity	Specificity
Asteria 2008	MP	86	20	94	81
Rubaltelli 2009	MP	51	22	82	88
Rago 2007	MP	92	34	97	100
Hong 2009	MP	145	34	88	90
Lyshchik 2005	MP	52	42	82	96
Friedrich-Rust 2009	MP	53	13	86	87
Tranquart 2008	MP	107	6	100	93
COMBINED		639	24%	92	90

MP = manual pressure

Electronical acoustic wave
Measurement of the shear-wave speed

SHEARWAVE ELASTOGRAPHY

Compression Force

shearwaves   shearwaves
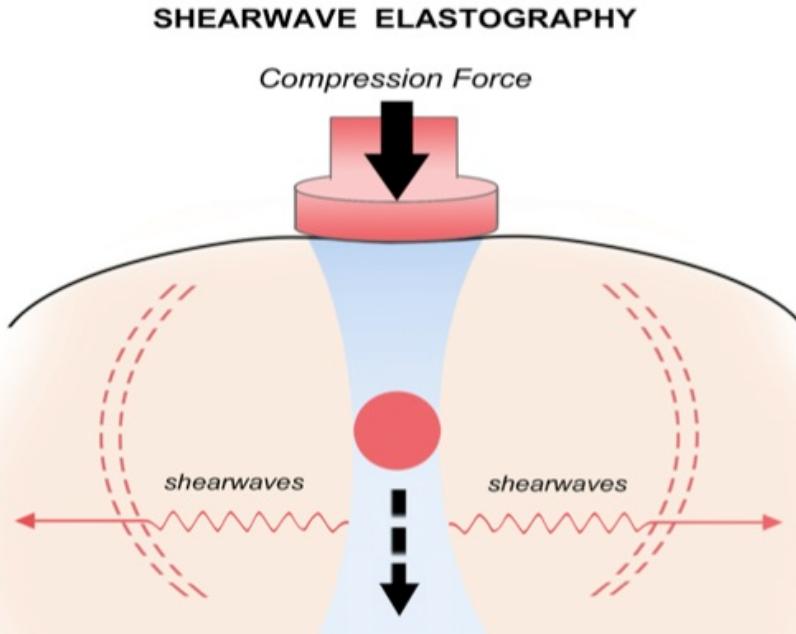
$$E = 3\rho V^2$$

E : Young's modulus
ρ : density of tissue
(1000kg/m3)
V : shear wave speed

Automatic compression pulses generated by the ultrasound probe and which induce transversely oriented shear-waves within tissue.

Shear waves
- travel faster in hard tissues
- are directly proportional to Young's modulus
- provide <u>quantitative information</u>.

Quantitative ROIs: Supersonic shearwave imaging (SSI)
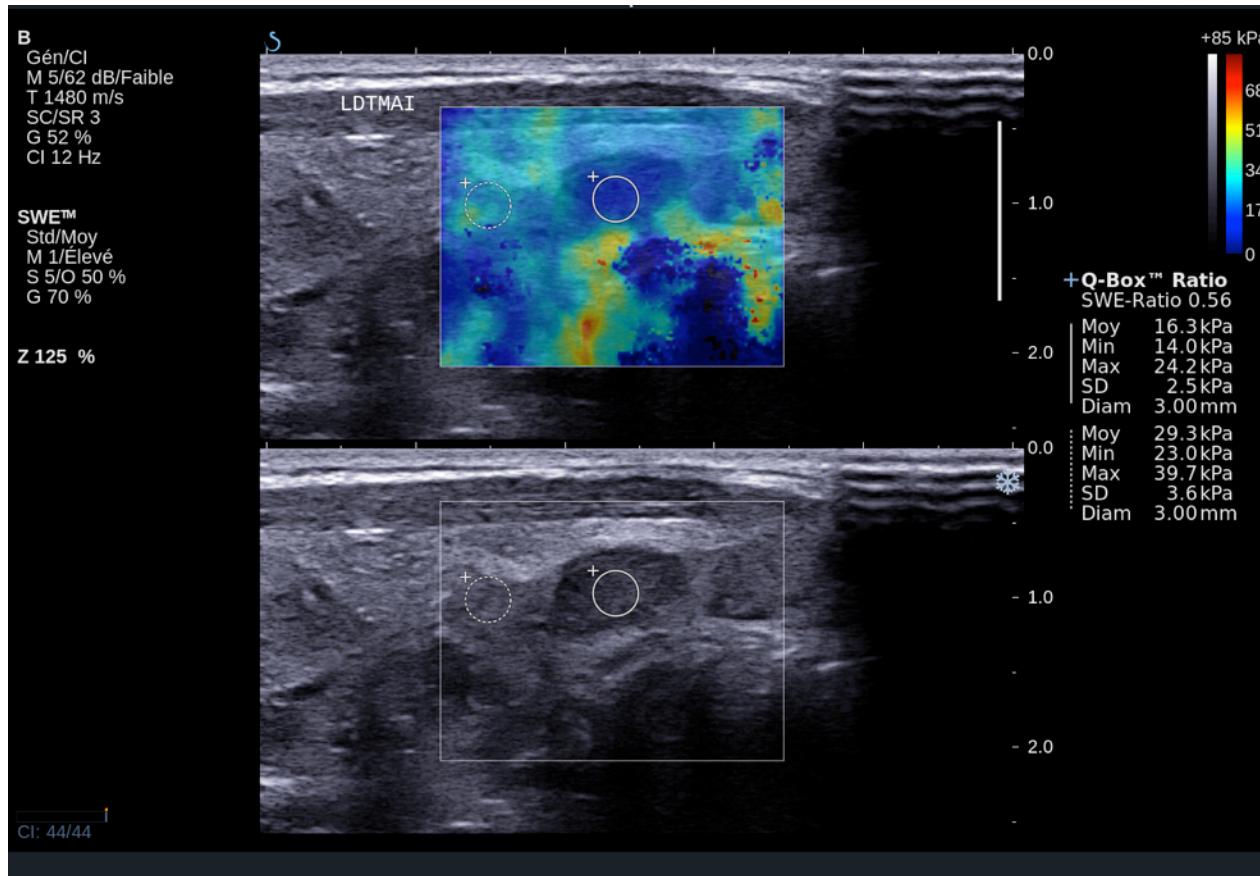
- Set one or two ROI, size and position adjustable retrospectively
- **Quantitative measurement** of the elasticity modulus expressed in kPa
- Absolute value and ratio available: cut-off value 65kPa (35kPa more recently)

Diagnostic value with SSI

Study	Nodules	Carcinomas (%)	Cut-off (kPa)	Sensitivity	Specificity	NPV	PPV
Sebag et al.	146	20	65	85	94	96	80
Bhatia et al.	81	21	35	77	71		

Shear Wave Elastography: A New Ultrasound Imaging Mode for the Differential Diagnosis of Benign and Malignant Thyroid Nodules

Sebag F. et al. J. Clin. Endocrinol. Metab. 2010 95:5281-5288

///

Shear Wave Elastography of thyroid nodules in routine clinical practice: preliminary observations and utility for detecting malignancy.

Bhatia KS et al. Eur Radiol. 2012 22(11):2397-406

US risk stratification

Why should we use US risk stratification?

- Increase in the number of nodules
- Rise in the number of FNAs: x3 between 1995 and 2005

**The main aims are to**

- Reduce the number of unnecessary US and FNAs
- Help select what patients should be operated on
- Enhance the inter-observer agreement of US reports

How to combine the signs for risk stratification?

US risk stratification

stiffness

Microcalcificazioni

Ipoecogenicità

Forma
(more tall than wide)

Margini
indistinti

Vascolarizzazione
Intralesionale e
caotica
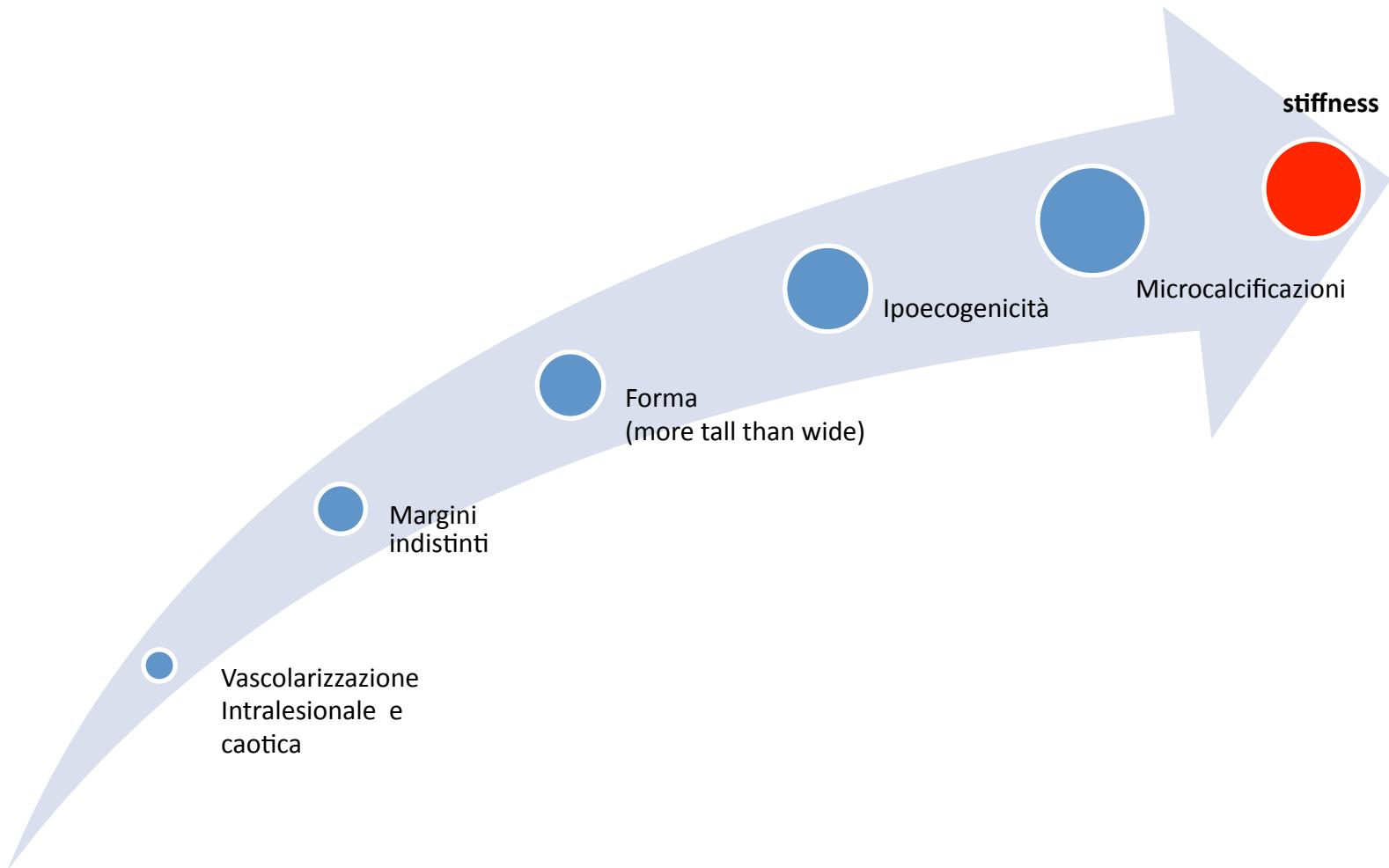
References for US risk stratification

- **Tae et al., Thyroid 2007;17(5) : 461.**
Diagnostic value of ultrasonography to distinguish between benign and
malignant lesions in the management of thyroid nodules.

- **Ito et al., Thyroid 2007; 17, 1269-1276**
Ultrasonographic evaluation of thyroid nodules in 900 patients: comparison
among ultrasonographic, cytological and histological findings.

- **Horvath et al., JCEM, may 2009, 90(5), 1748-51**
An ultrasonogram reporting system for thyroid nodules stratifying cancer risk for clinical
management.

- **Park et al., Thyroid 2009, 19 (11), 257-64**
A proposal for a thyroid imaging reporting and data system for ultrasound features of thyroid
carcinoma.

- **Kwak et al., Radiology 2011; 260; 892-99**
Thyroid Imaging Reporting and Data System for US features of nodules. A step in establishing
better stratification of cancer risk.

- **Kwak et al., Korean J Radiol 2013; 14(1): 110-117**
Image reporting and characterization system for US features of thyroid nodules: multicentric
korean retrospective study

Risk stratification systems

2009
HORVATH et al.
10 PATTERNS

6-POINT SCALE

2009-2013
KOREAN GROUPS

5-7-POINT SCALES

2007
THE GRADING
SYSTEM
TAE et al.
ITO et al.

QUALITATIVE
ASSESSMENT

**QUANTITATIVE
RISK
STRATIFICATION**

2011-2013

Russ team

6-POINT SCALE
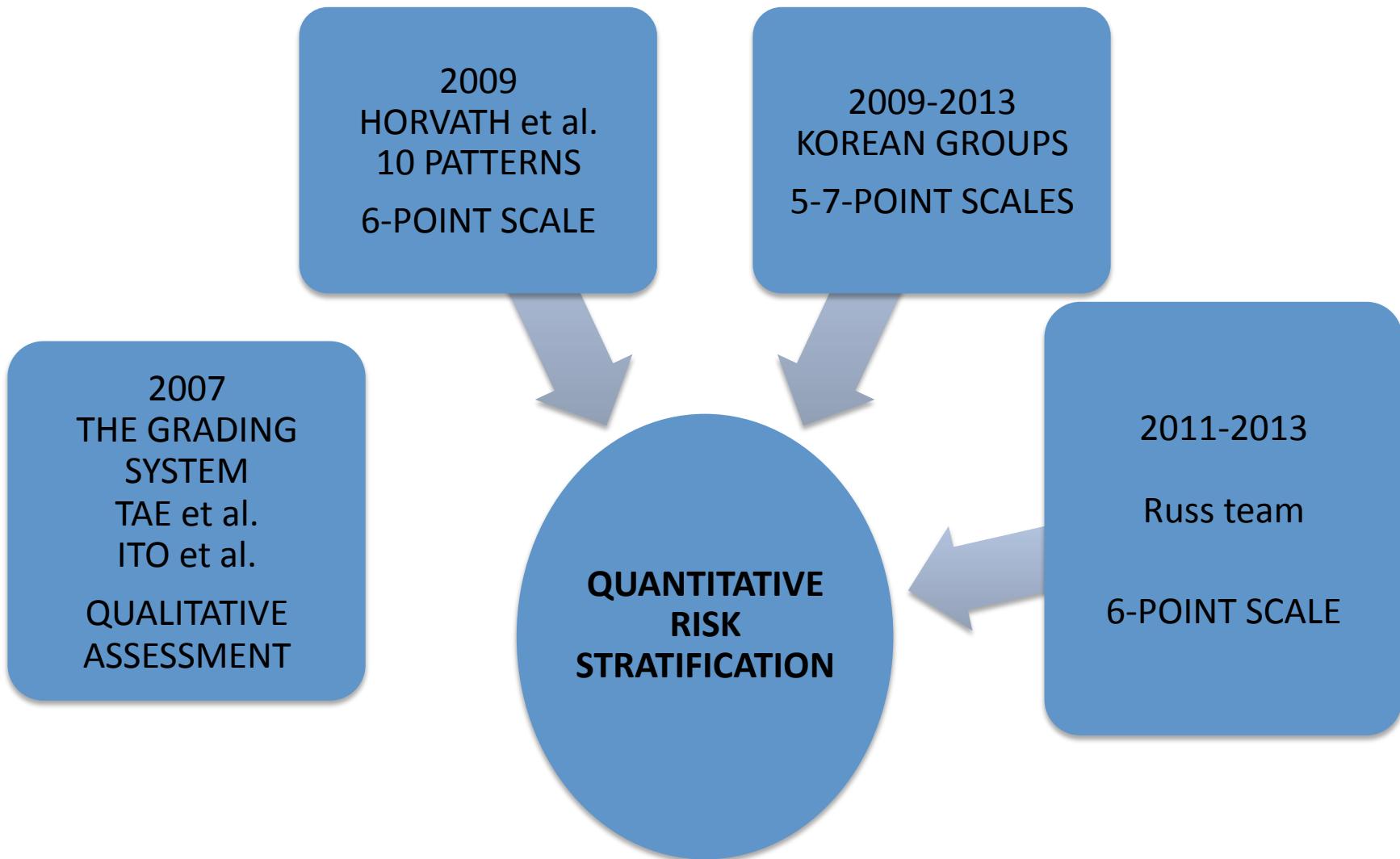
A useful ultrasound score to select thyroid nodules requiring fine needle aspiration in an iodine-deficient area

A. Cavaliere[1]*, R. Colella[1]*, E. Puxeddu[2], G. Gambelunghe[2], A. Falorni[2], F. Stracci[3], M. d'Ajello[4], N. Avenia[4], and P. De Feo[2]
[1]Institute of Pathological Anatomy; [2]Department of Internal Medicine; [3]Department of Hygiene; [4]Regional Referral Centre for Endocrine Surgery, Perugia University, Perugia, Italy

The high prevalence of thyroid nodules in iodine-deficient areas is a practical problem because of the large number of patients requiring fine needle aspiration (FNA) to detect malignant nodules. AIM: To obtain an ultrasound (US) score for predicting malignant nodules and reduce the number of unnecessary and expensive FNA.

Table 1 - Frequency distribution of non-neoplastic and malignant nodules for single ultrasound parameters (no. 2801).

		Cytologic diagnosis			
		Non-neoplastic (Thy 2)		Suspicious of malignancy and diagnostic of malignancy (Thy 4-5)	
	No.	No.	(%)	No.	(%)	p (χ^2)
No. of nodules						
Single	984	950	(96.5)	34	(3.5)	0.000
Multiple	1817	1792	(98.6)	25	(1.4)	(12.395)
Echostructure						
Solid	1522	1484	(97.5)	38	(2.5)	0.151
Mixed/liquid	1279	1258	(98.4)	21	(1.6)	(2.066)
Echogenicity						
Hypo	1644	1597	(97.1)	47	(2.9)	0.002
Hyper/Iso/Ane	1157	1145	(99.0)	12	(1.0)	(10.064)
Halo						
Incomplete or absent	814	779	(95.7)	35	(4.3)	0.000
Present	1987	1963	(98.8)	24	(1.2)	(25.293)
Microcalcifications						
Present	1740	1695	(97.4)	45	(2.6)	0.033
Absent	1061	1047	(98.7)	14	(1.3)	(4.533)
ØAP/ØTR						
≥1	303	291	(96.0)	12	(4.0)	0.030
<1	2498	2451	(98.1)	47	(1.9)	(4.700)
Vascularization						
Type III*	2131	2090	(98.1)	41	(1.9)	0.266
TYPR II/I**	670	652	(97.3)	18	(2.7)	(1.239)

**Type I vascularization applies to nodules without vascularization, **Type II to nodules with external vascularization, *Type III to nodules with both internal and external vascularization. AP: antero-posterior; TR: transversal.

The TI-RADS concept

CLINICAL STUDY

Prospective evaluation of thyroid imaging reporting and data system on 4550 nodules with and without elastography

Gilles Russ[1,2], Bénédicte Royer[1,3], Claude Bigorgne[1], Agnès Rouxel[1,2], Marie Bienvenu-Perrard[1,4] and Laurence Leenhardt[1,2]

Design: prospective comparative study (4550 nodules)

Assess diagnostic accuracy of the TI-RADS score using:
- gray-scale US alone (3658)
- elastography alone (Toshiba Applio) (991)
- the combination of gray-scale score + elastography (1305)

Compared with cytological results and histological results (263 cases included 133 carcinomas).

TI-RADS SCORE	Risk stratification of malignancy
1	NORMAL EXAMINATION
2	BENIGN
3	VERY PROBABLY BENIGN
4A	LOW RISK OF MALIGNANCY
4B	HIGH RISK OF MALIGNANCY
5	PRACTICALLY CERTAINLY MALIGNANT

SUSPECT PATTERNS

HIGHLY SUSPECT

- Irregular shape taller-than-wide
- Irregular borders
- Microcalcifications
- Markedly hypoechoic

- **High stiffness with elastography**

MILDLY SUSPECT

- No sign of high suspicion
- Mildly hypoechoic

- 3 to 5 signs and/or
- Metastatic lymph node

TI-RADS
SCORE 5

- 1 or 2 signs
- No metastatic lymph node

TI-RADS
SCORE 4B

TI-RADS
SCORE 4A

TIRADS 4A + 4B+ 5 = 95.7% of carcinomas

BENIGN PATTERNS

VERY PROBABLY

- No sign of high suspicion

AND

- Isoechoic or Hyperechoic

CONSTANTLY

- Simple cyst
- Spongiform nodule
- "White knight"
- Isolated macrocalcification
- Nodular hyperplasia

TI-RADS
SCORE 3

TI-RADS
SCORE 2

92% of TIRADS scores 2+3 were benign
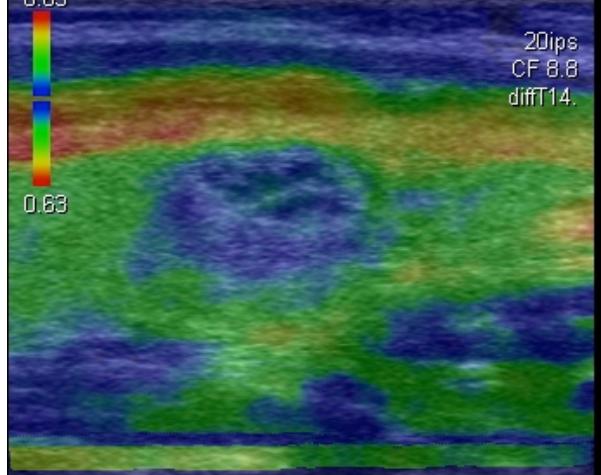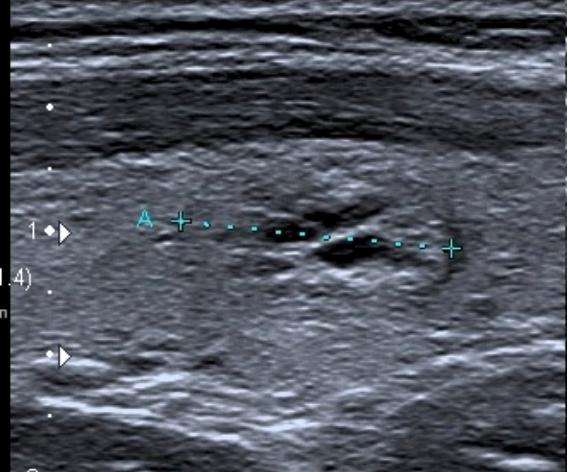
CONCLUSION 1

**TAKEN SEPARATELY, STIFFNESS HAS THE BEST SENSITIVITY/
SPECIFICITY COMPROMISE
FOR THE DETECTION OF CARCINOMAS
COMPARED TO ALL OTHER US SIGNS**

**COULD IT REPLACE COMPLETELY
US GRAY-SCALE AND DOPPLER IMAGING ?**

Raising sensitivity

- Sensitivity of US signs alone: 85%

- Sensitivity of elastography alone: 81%

- Sensitivity of the combination: 97%

Parameter	Se	Sp
Hypoechogenicity	72	60
Microcalcifications	31	98
Irregular margins	25	99
Intranodular vascularization	37	88
More tall than wide	14	99
At least one of five US-CFD	85	54
RTE III or IV	81	62
At least one of six US-CFD-RTE	97	34

CONCLUSION 2
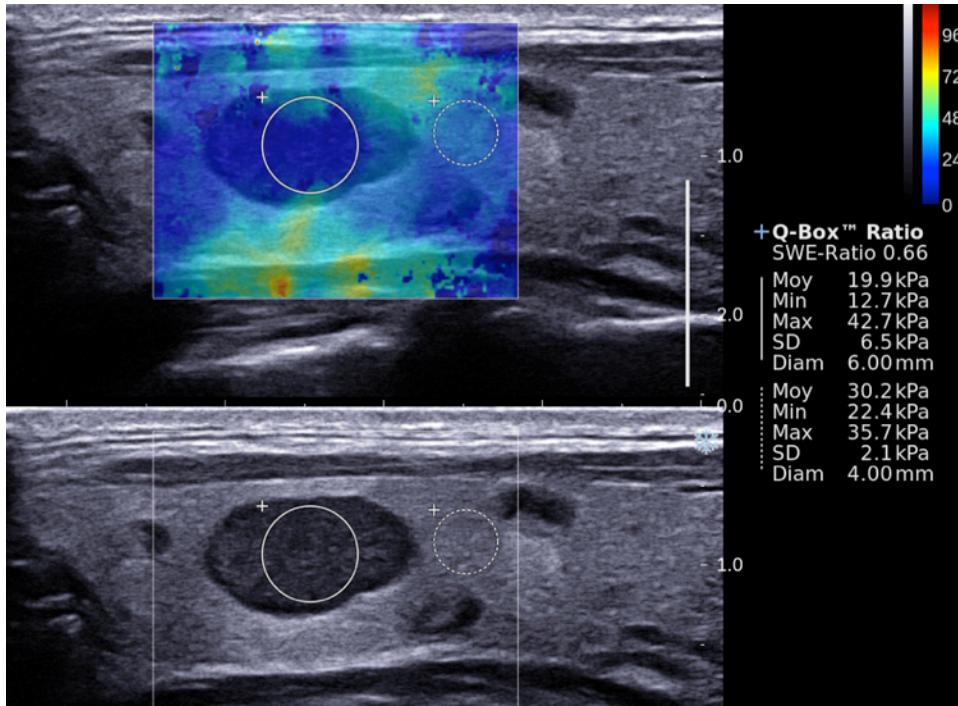
THEREFORE ELASTOGRAPHY CANNOT BE USED ALONE AND CANNOT REPLACE US GRAY-SCALE AND COLOR IMAGING

UN PO' DI BUON SENSO

• L'elastografia è parte dello studio ecografico e non lo sostituisce; i risultati vanno sempre integrati con i dati clinico anamnestici.

• Uno studio ecografico completo e ben fatto può e deve ridurre il numero degli agoaspirati.

• L'esame citologico, con i limiti propri della metodica, resta comunque a tutt'oggi il gold standard della diagnostica.

US GRAY-SCALE AND ELASTOGRAPHIC PATTERN

SUSPICIOUS
(At least 1 sign)
Malignancy risk 6%-100%

- Irregular shape
- Irregular borders
- Microcalcifications
- Hypoechoic solid
- **High stiffness**

PROBABLY BENIGN
Malignancy risk<1/400

- No sign of suspicion
- **Low stiffness**

FNA advised
if size≥8-10mm

Estimated
reduction
of
unecessary
FNAs ≥34%

No FNA
unless proven
growth with US
and > 10mm

Take home messages

1. A hard nodule should always be considered as suspicious but a carcinoma can be soft.

2. Elastography cannot be used alone and cannot replace US gray-scale or Doppler.

3. It should be integrated with these techniques in a decision flowchart to optimize the selection of nodules that should undergo FNA.

4. It can be used to raise sensitivity or specificity of conventional US.

5. Quantitative methods have a better inter-observer agreement. SSI is the fastest.

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