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3

OBJECTIVES

- Discuss the **physiology** of vascularization of **malignant lesions**
- Understand Doppler findings suggestive of malignant and benign lesions with **waveform analysis**
- Consider how assessment of lesions may differ by **location** in the body
- Review **Doppler optimization** for evaluating small lesions

4

IMAGING PATHOLOGY

What do we do when we encounter pathology?

Images from personal files of Wiencek E. (on file with author)

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IMAGING PATH

- Sagittal
- Transverse
- Measure
- Color
- Done!

Images from personal files of Wiencek E. (on file with author)

6

YOU CAN EVEN GET IT ON A T-SHIRT

7

BUT WHAT IF WE WENT A STEP FURTHER?

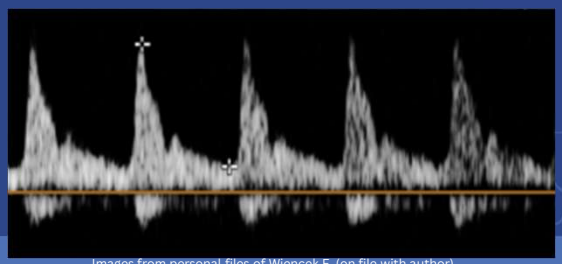
8

CAN SPECTRAL DOPPLER AID IN DIFFERENTIATING MALIGNANT VS. BENIGN LESIONS

9

SPECTRAL DOPPLER ANALYSIS

- Color shows presence of flow
- Spectral shows us characteristics of flow
- In healthy arterial vessels we can derive information of the blood supply, and demand of distal tissues



Images from personal files of Wiencek E. (on file with author)

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VASCULAR CHARACTERISTICS

- If spectral doppler gives us information about the function and demands of the tissues the vessels are feeding, can we use this information to differentiate between benign and malignant lesions?

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1

THE ANSWER:

Yes! But why?

- Malignant tissues differ from other tissues in the body
- Their vascularization is also different, which creates characteristics that are detectable using spectral doppler analysis

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MALIGNANT VASCULARIZATION

- In order to proliferate, cancers need oxygen and nutrients
- To satisfy this need, they need vascular supply

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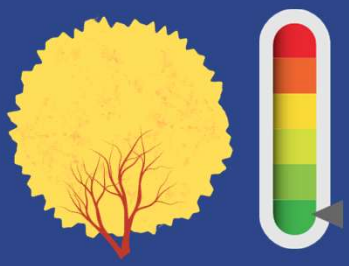
MALIGNANT VASCULARIZATION

- When cancers are small, they don't need a lot of vascular supply
- When they grow bigger, the oxygen gradient is diminished, and cells farther away from blood vessels are hypoxic



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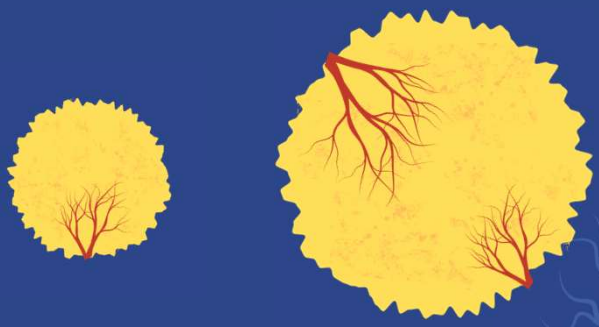
MALIGNANT VASCULARIZATION

- In order to grow bigger, cancers secure vascular supply through a process called

Angiogenesis



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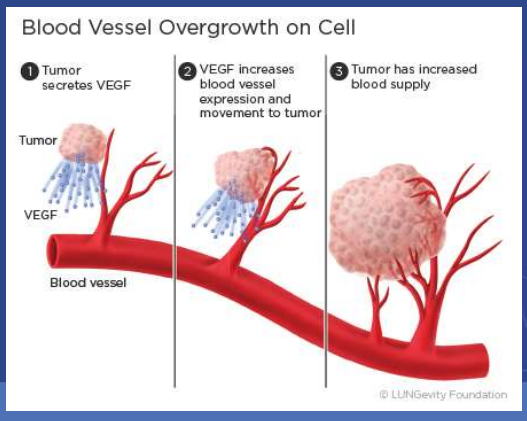
ANGIOGENESIS

angio- (vessel) + genesis (birth, origin): formation of new blood vessels

Tumor sends out a pro-angiogenic chemical signals to derive blood supply for itself

- Commonly vascular endothelial growth factor (VEGF)

2



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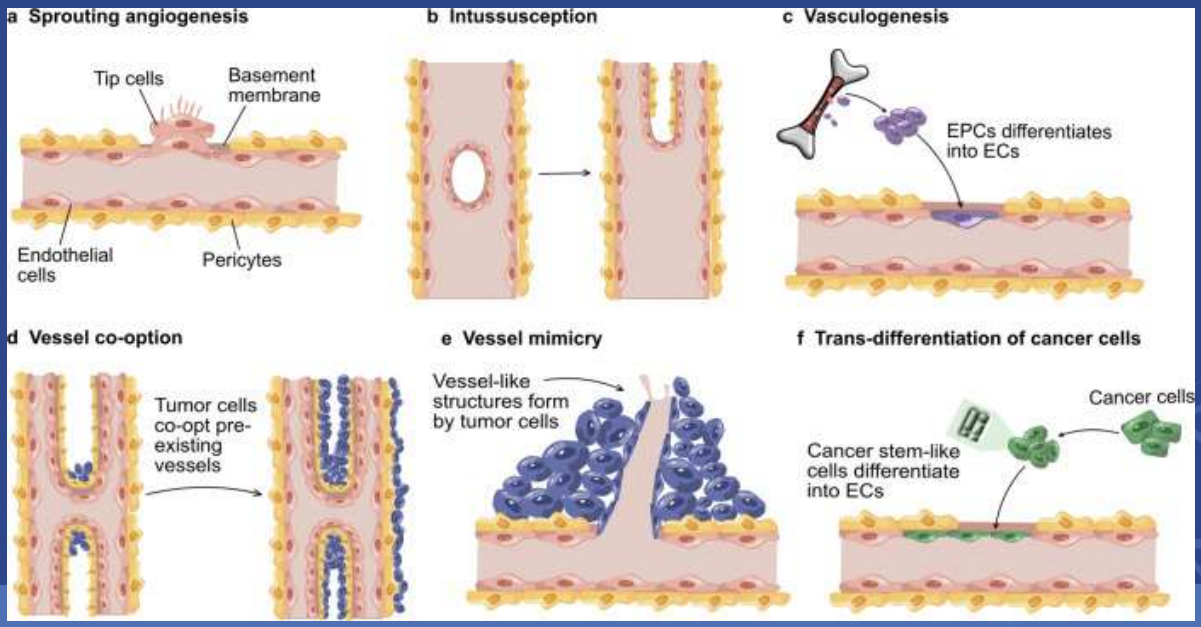
METHODS OF ANGIOGENESIS



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ANGIOGENESIS

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- Angiogenesis happens naturally in the body
- Slow process that eventually creates a complete mature vascular network
- Important for:
  - Wound healing
  - Formation of collateral vessels
  - Menstrual cycle

18

1

MALIGNANT ANGIOGENESIS

- In malignant neovascularization, there is an
  - over-expression of pro-angiogenic factors &
  - inactivation of anti-angiogenic factors
- Angiogenesis occurs rapidly creating disordered vascular networks
- As cancer cells chaotically and rapidly proliferate, so do the vessels that feed them

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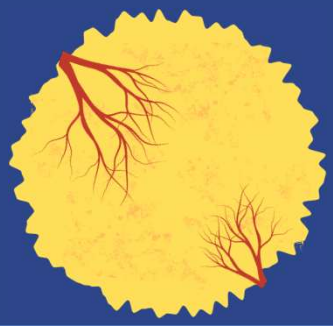
1

TUMOR MICROENVIRONMENT

Hypertrophic tumor tissue and chaotic vascularity leads to…

- lack of lymphatic drainage (increased interstitial pressure)
- deformed vessels (hinder blood flow and nutrient delivery)

HIGH PRESSURE



HYPOXIC

20

TUMOR MICROENVIRONMENT

1

ABNORMAL VESSELS
- Leaky
- Hypoxic

Inadequate blood supply → More vessels to compensate

ABNORMAL ARCHITECTURE
- High interstitial pressure
  Normal: 0–3 mmHg
  Tumors: 5–40 mmHg

Resistive tumor environment → High **RI**

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SONOGRAPHICALLY…

MALIGNANT LESIONS ARE

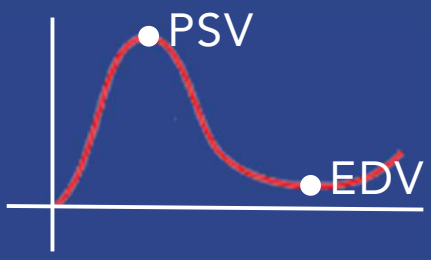
22

3

RESISTIVE INDEX

How easily blood is permitted to flow through vessels

$$\text{Resistive Index} = \frac{\text{(Peak Systolic Velocity - End Diastolic Velocity)}}{\text{Peak Systolic Velocity}}$$



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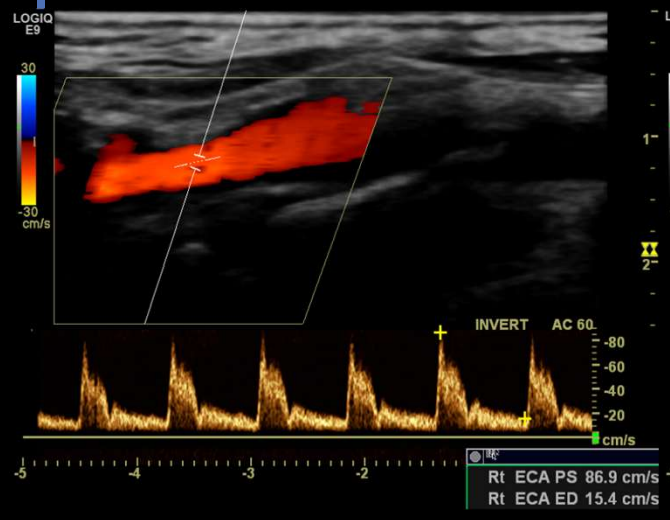
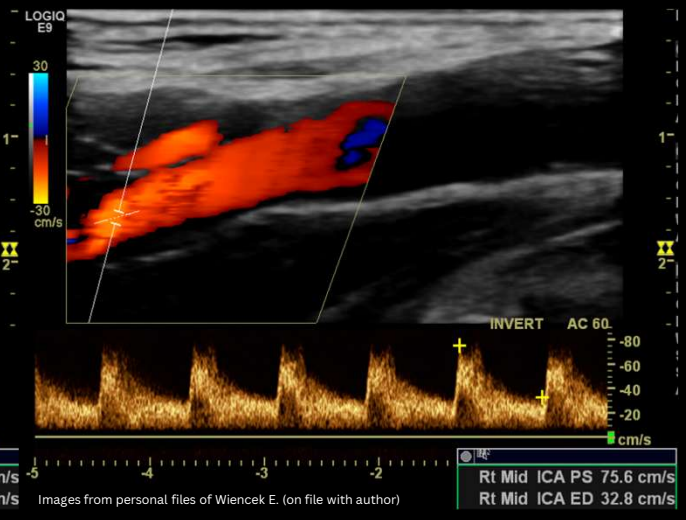
ECA (HIGH RI) VS. ICA (LOW RI)



Higher Resistivity



Images from personal files of Wiencek E. (on file with author)

Lower Resistivity

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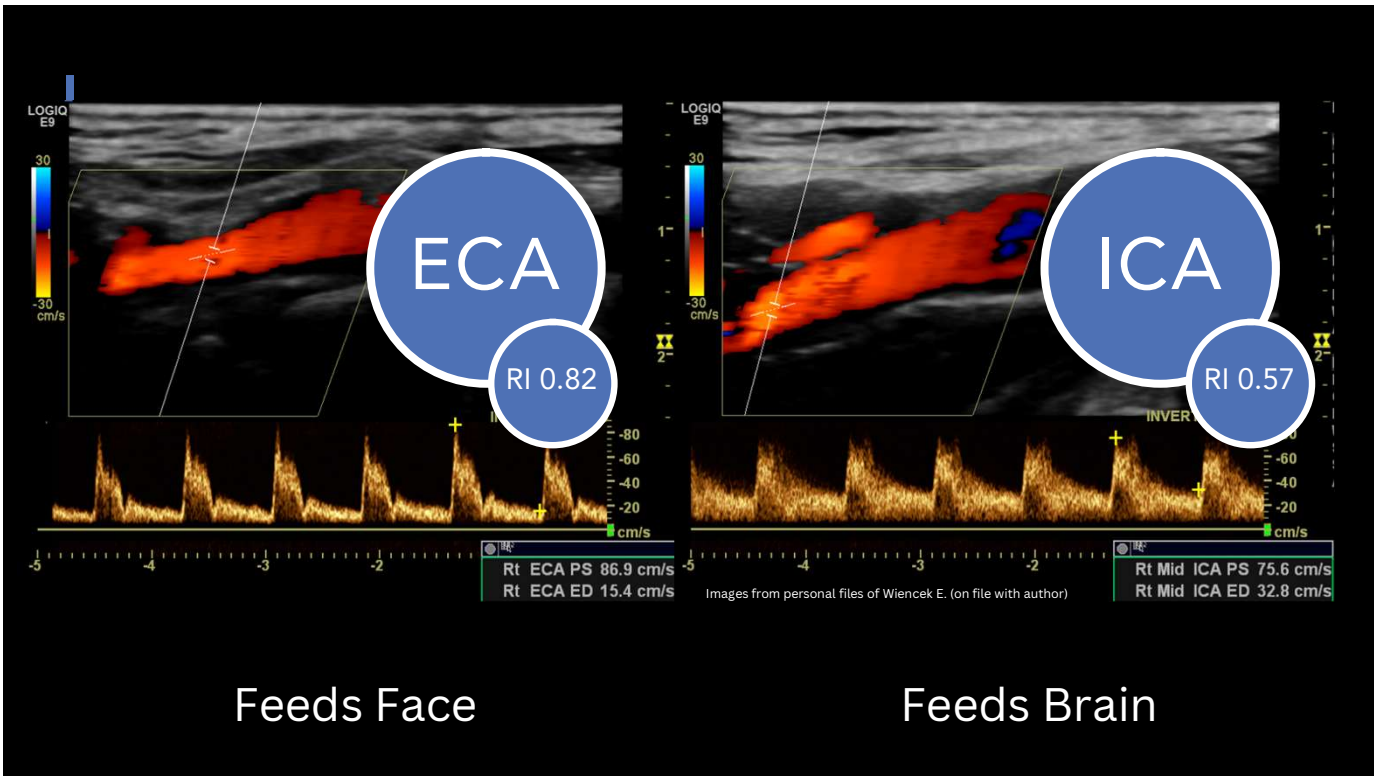

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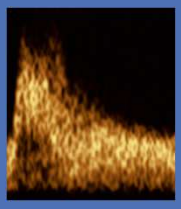
VASCULAR RESISTANCE

Normal Tissues

increased demand = vasodilation

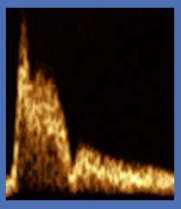
Variable Resistance



Malignant Tissues

increased demand = increased vessels

High Resistance



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WHERE IS THIS APPLICABLE?

- Thyroid
- Breast
- Liver
- Ovaries

Lets look at the most recent literature...

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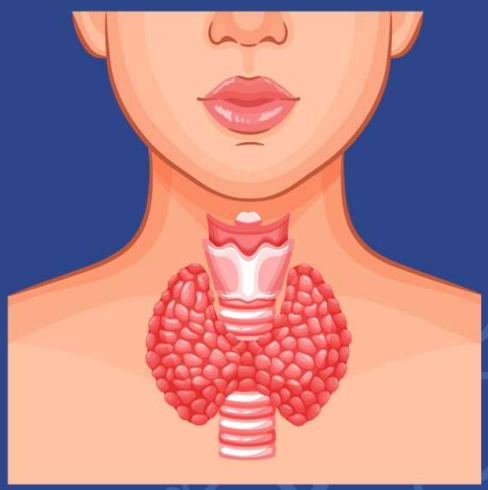
4

THYROID NODULES

RI > 0.73 indicates malignancy

sensitivity: 81.3%
specificity: 76.9%



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THYROID NODULES

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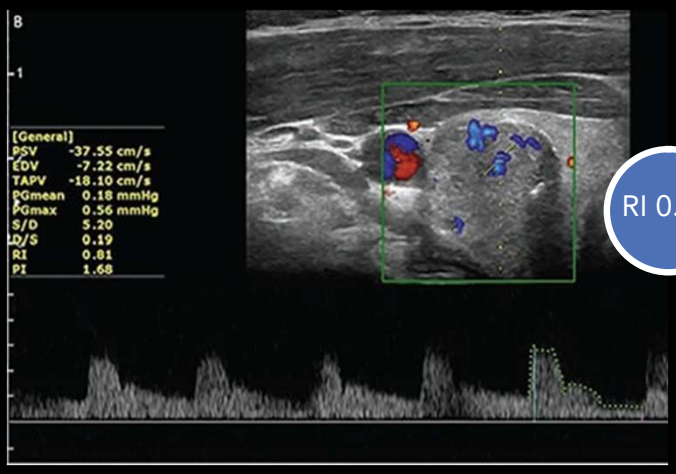
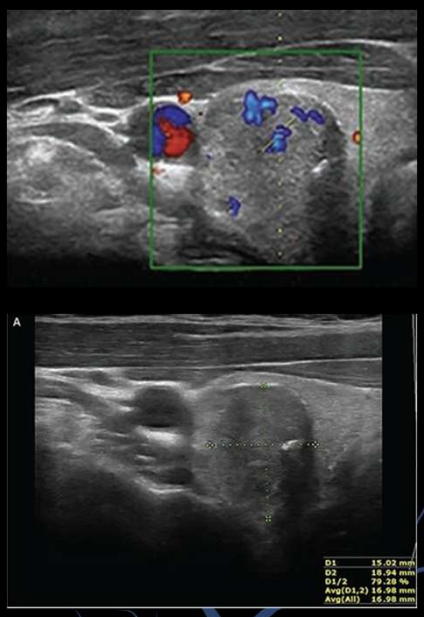


RI 0.81



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THYROID NODULES

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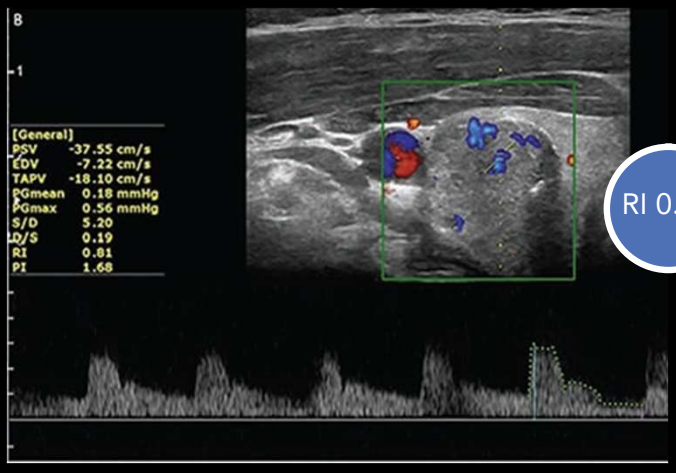
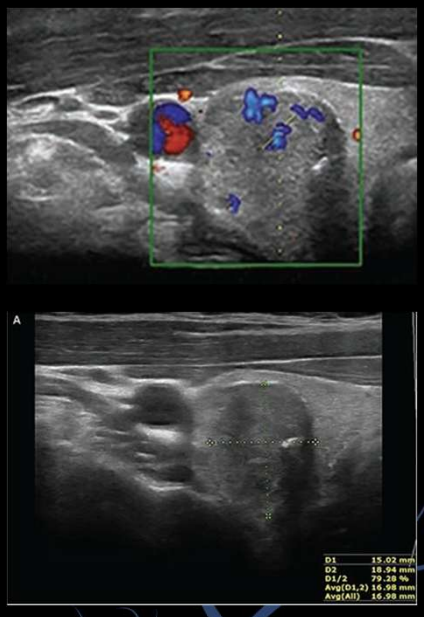
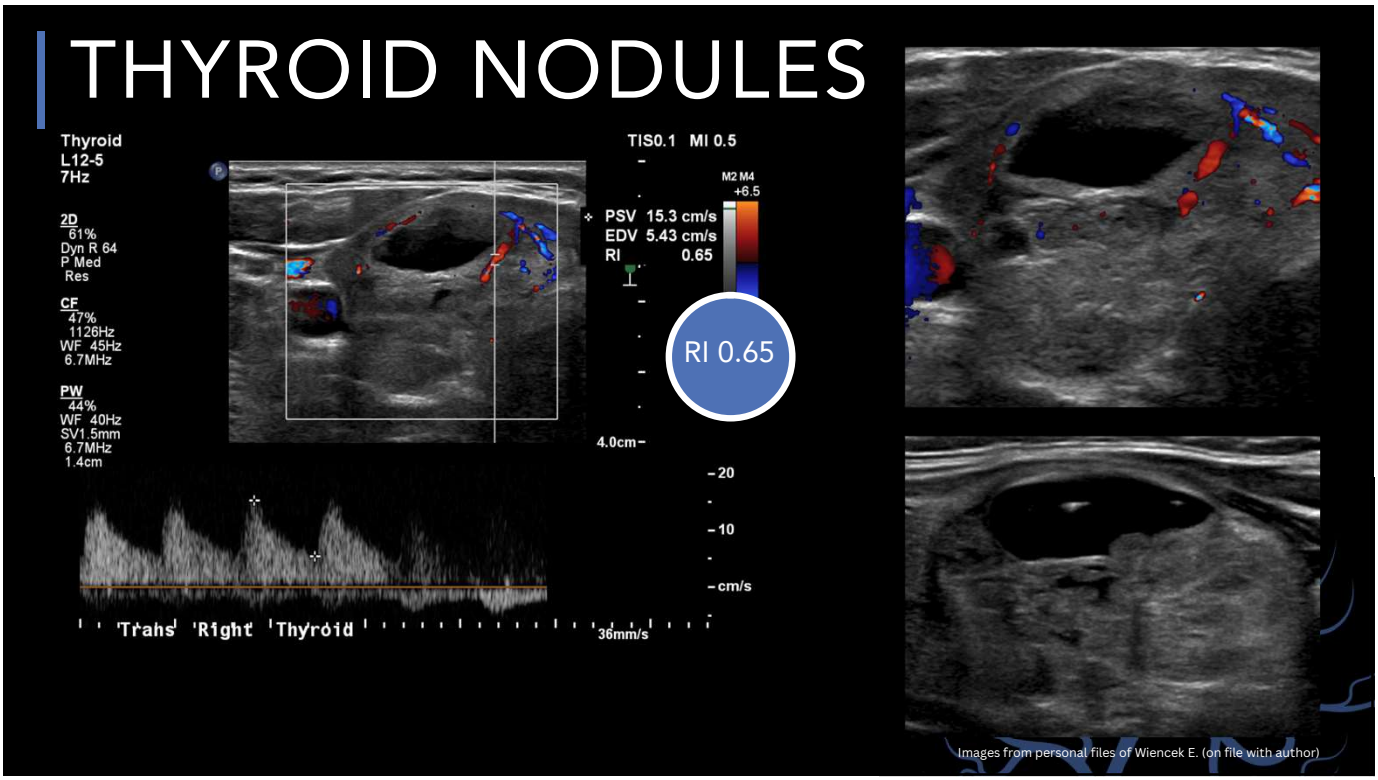


RI 0.81



Malignant Nodule

30



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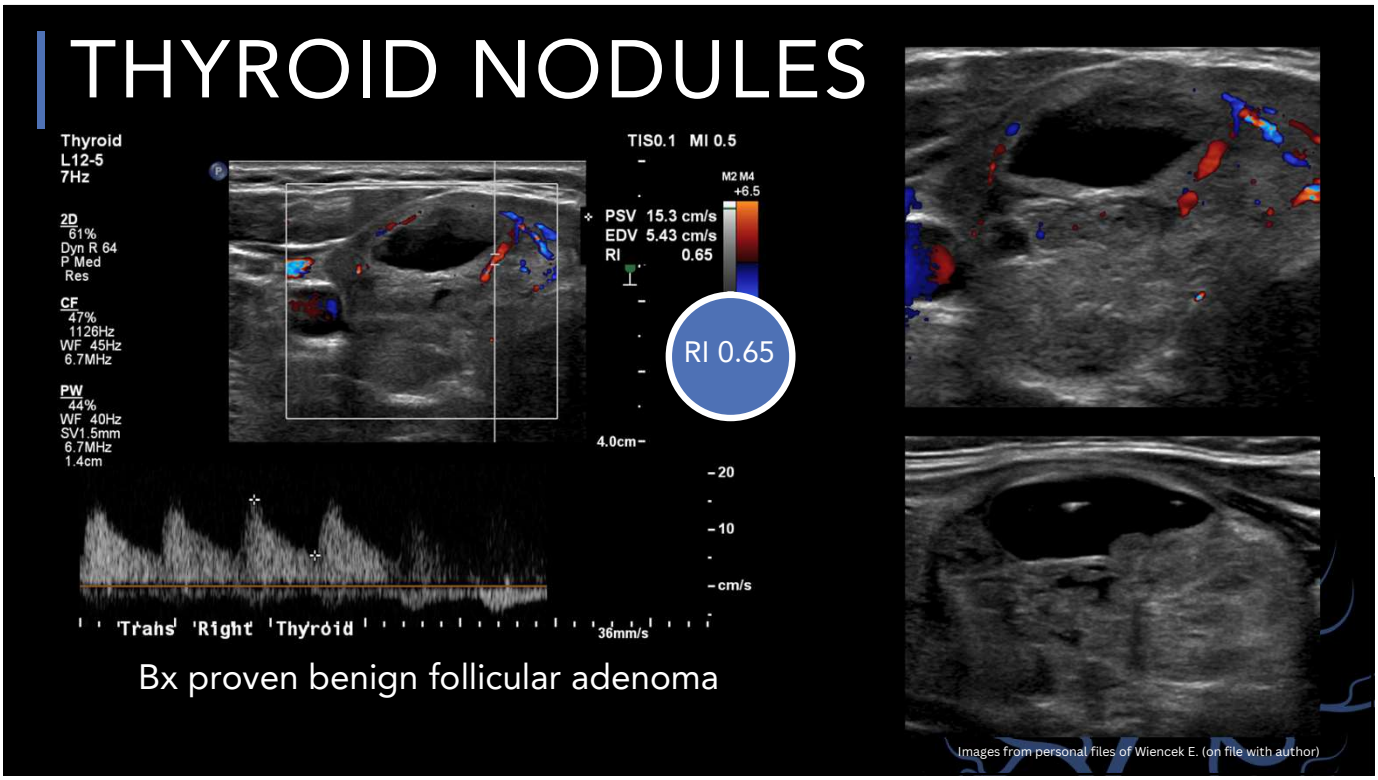

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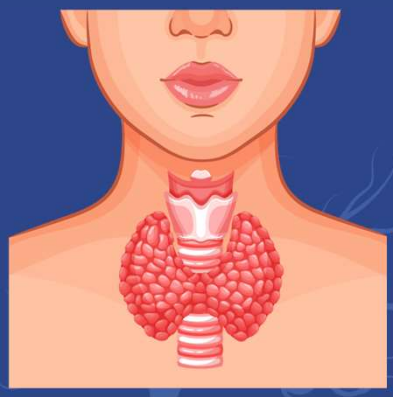
4

FUTURE APPLICATIONS

- Help with risk stratification & clinical management
- Tracking changes in vascularity and flow over time
- Monitoring the response to treatment (radiofrequency ablation)



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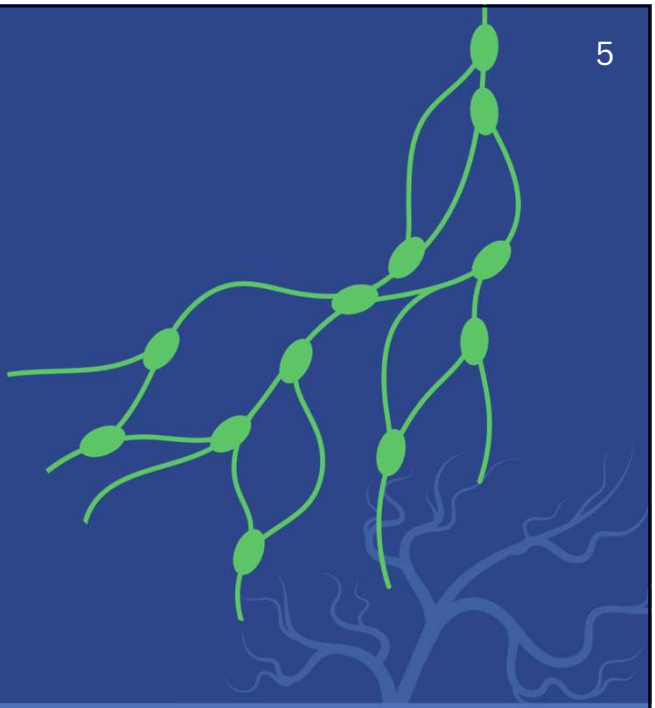
LYMPH NODES

RI >0.69 indicates malignancy

sensitivity: 78%
specificity: 100%



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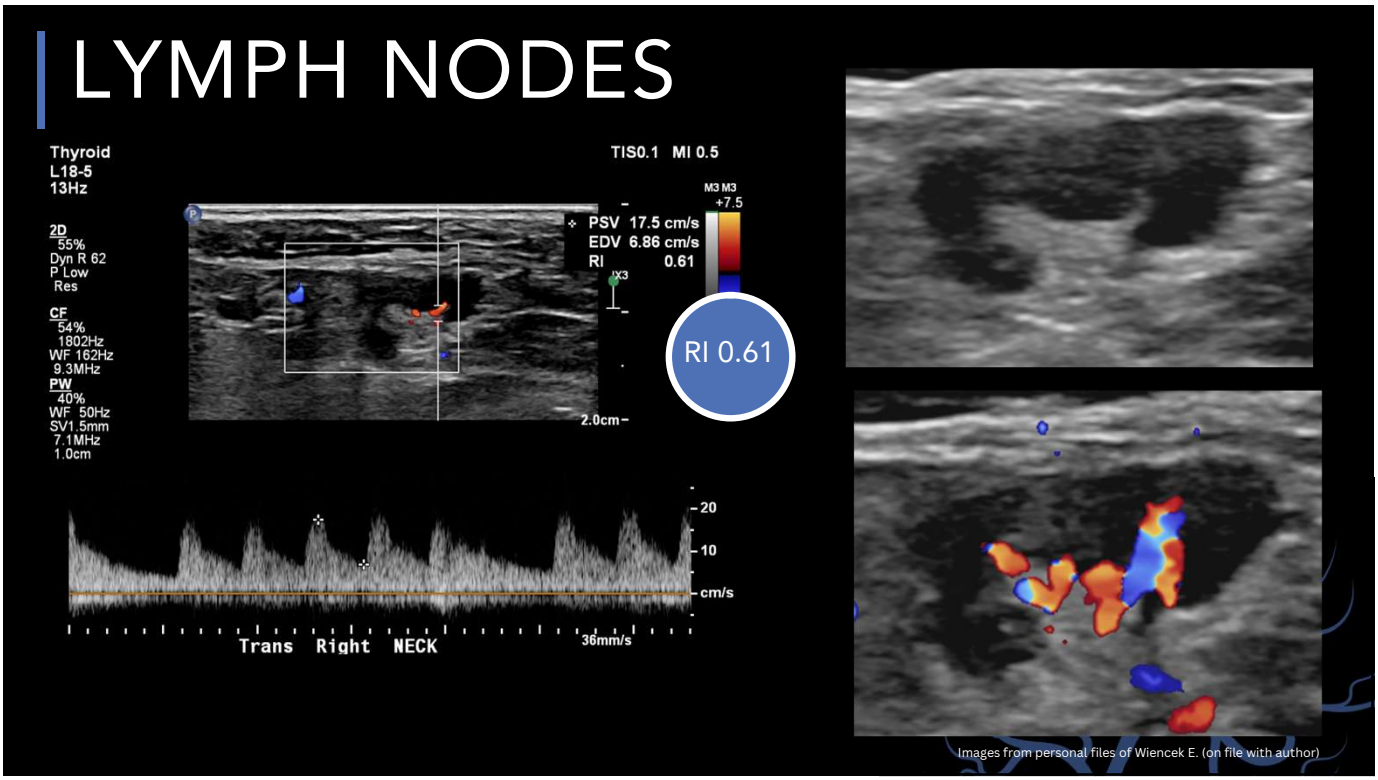
LYMPH NODES



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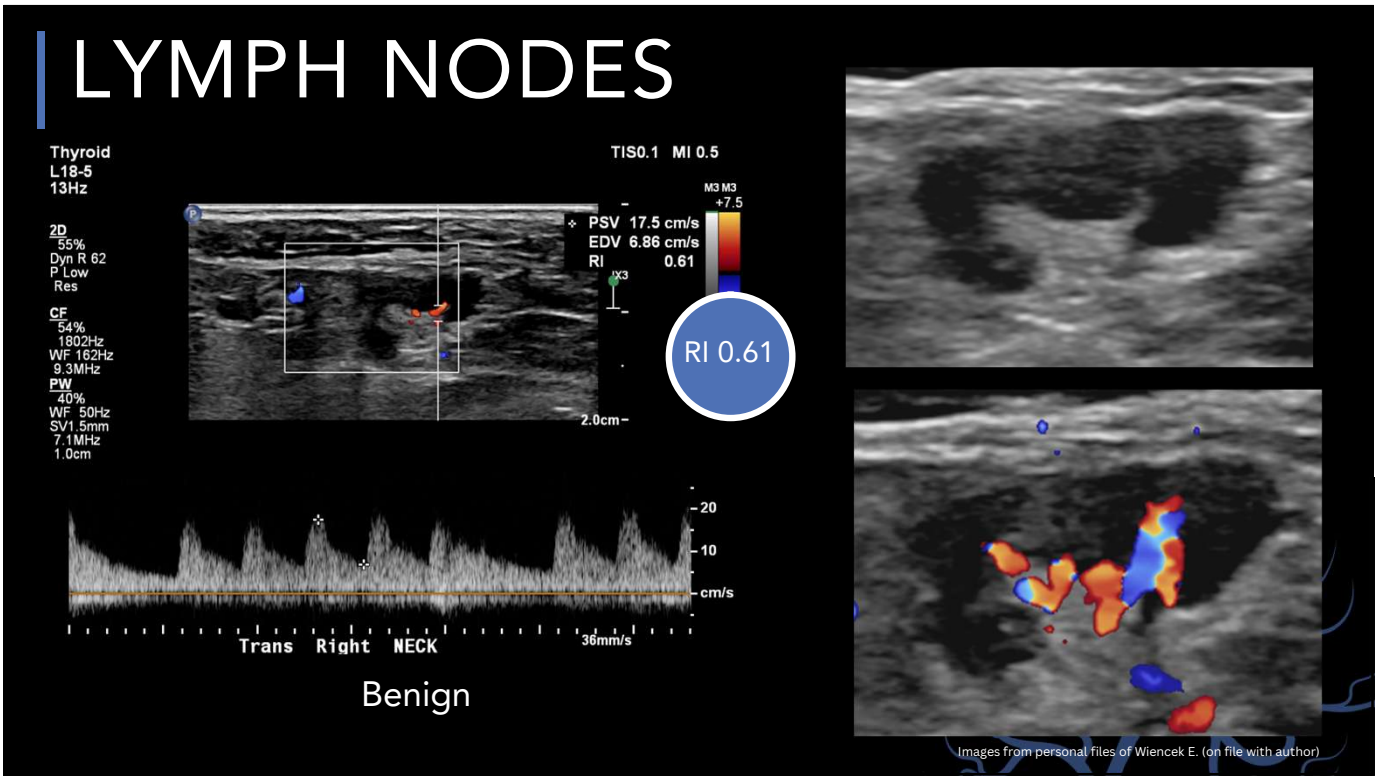
LYMPH NODES



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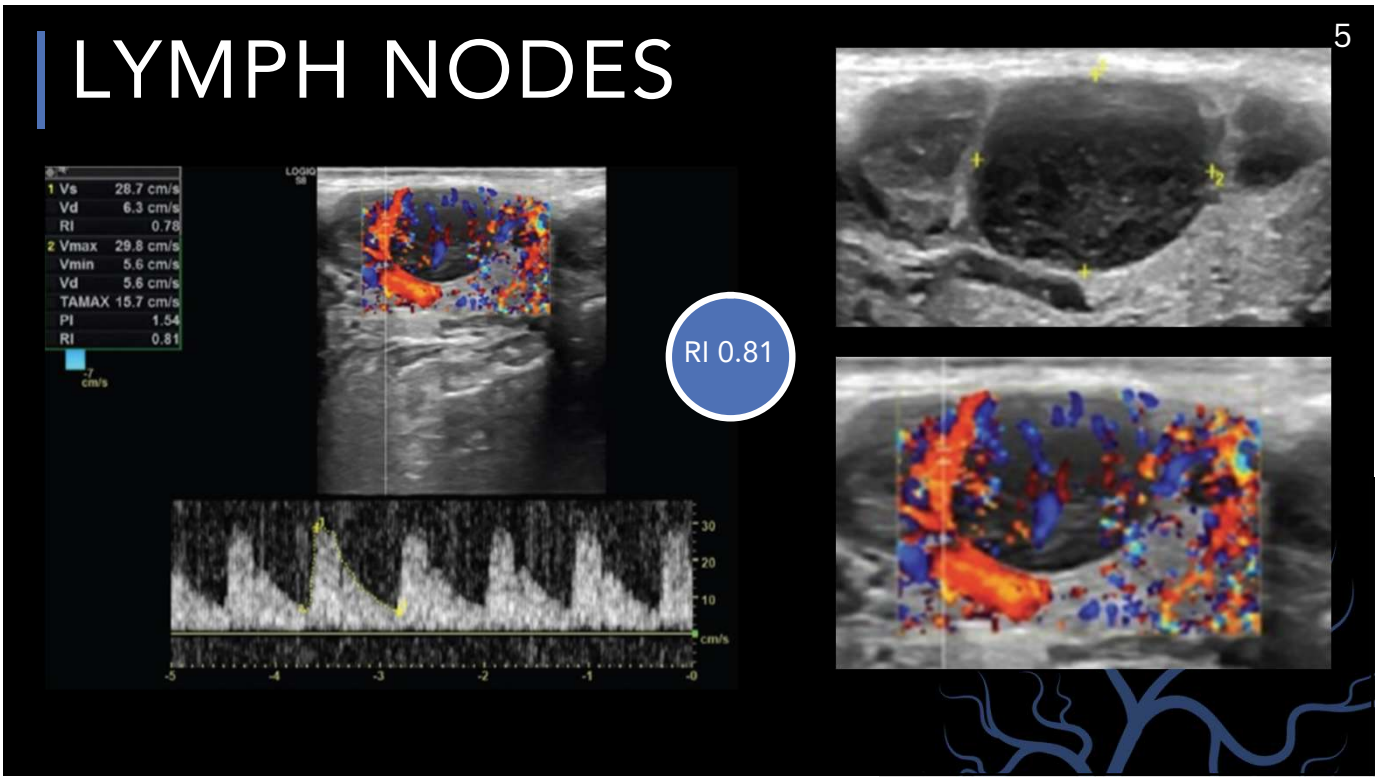

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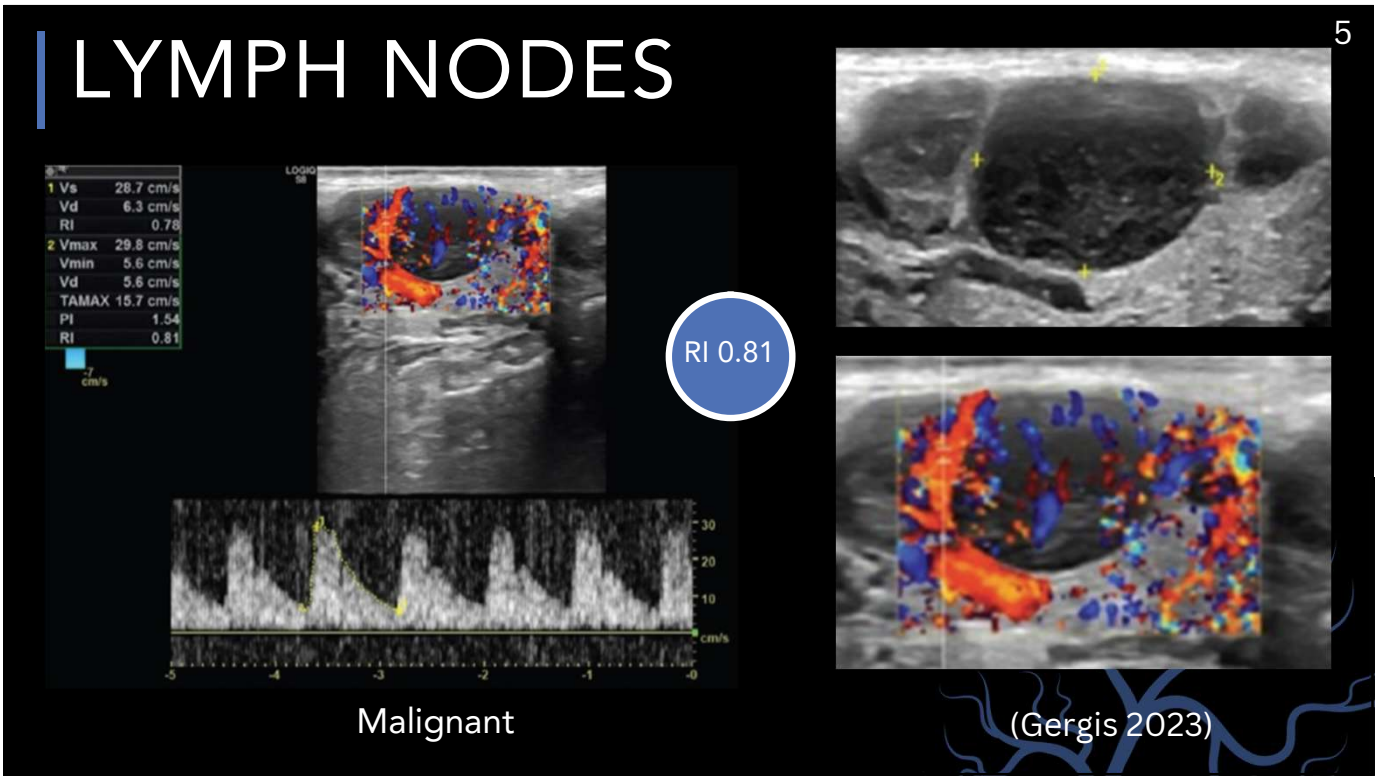

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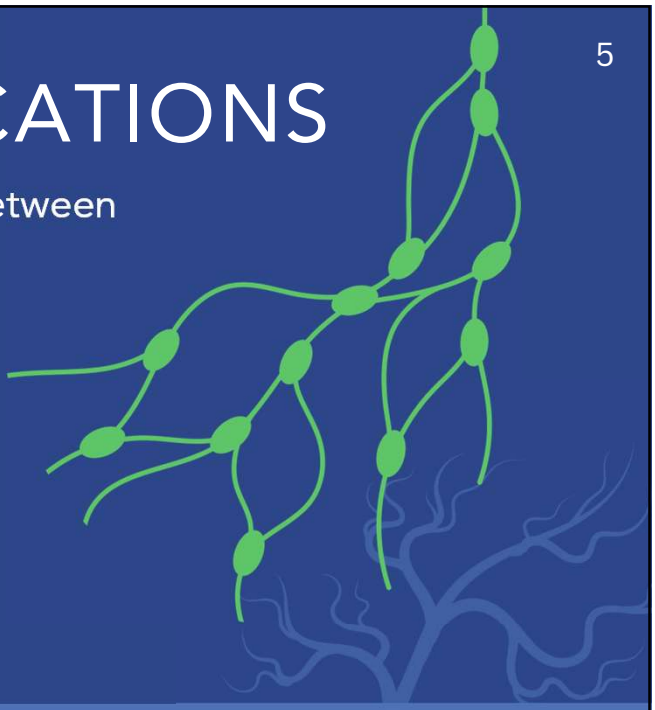
5

FUTURE APPLICATIONS

- Reliable tool to differentiate between benign and malignant nodes
- May reduce need for histopathological analysis



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6

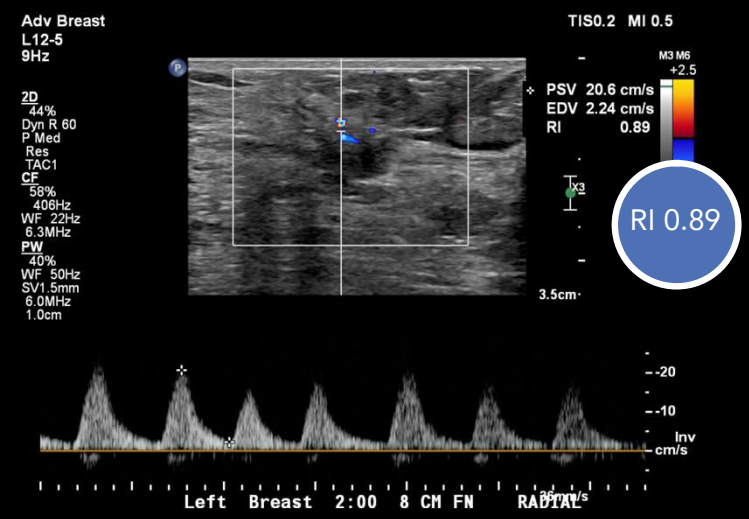
BREAST LESIONS

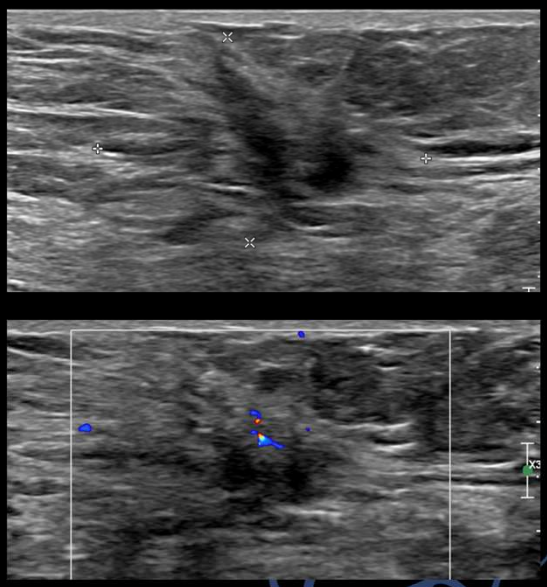
RI > 0.65 indicates malignancy

sensitivity: 84%
specificity: 83%

40

BREAST LESIONS





Images from personal files of Wiencek E. (on file with author)

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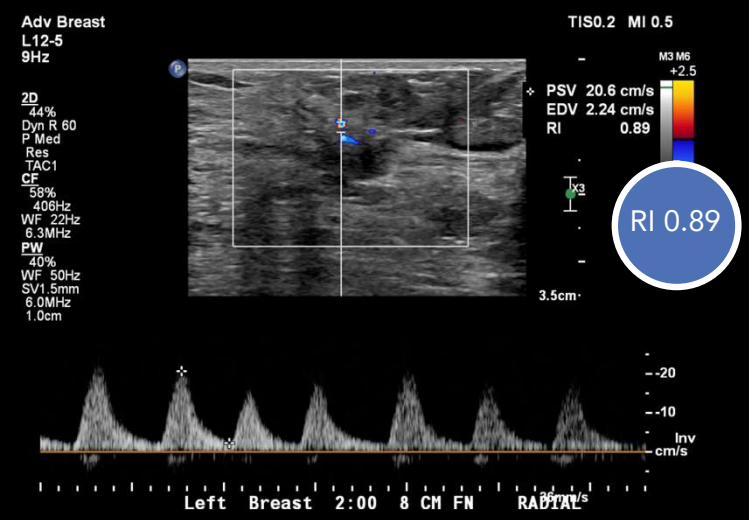
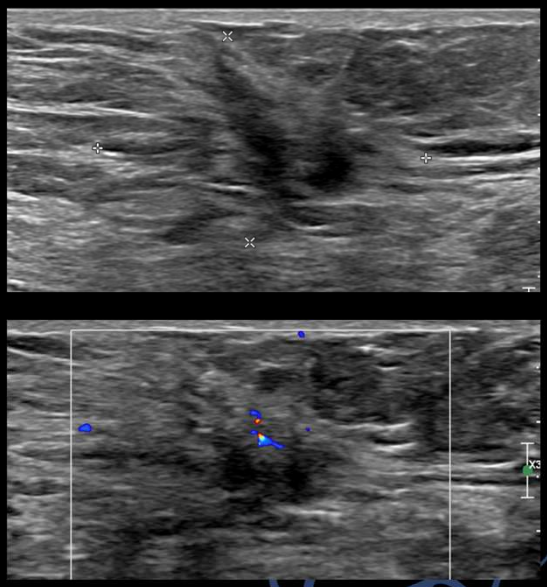
BREAST LESIONS





Bx proven Invasive ductal carcinoma with focal ductal carcinoma in situ

Images from personal files of Wiencek E. (on file with author)

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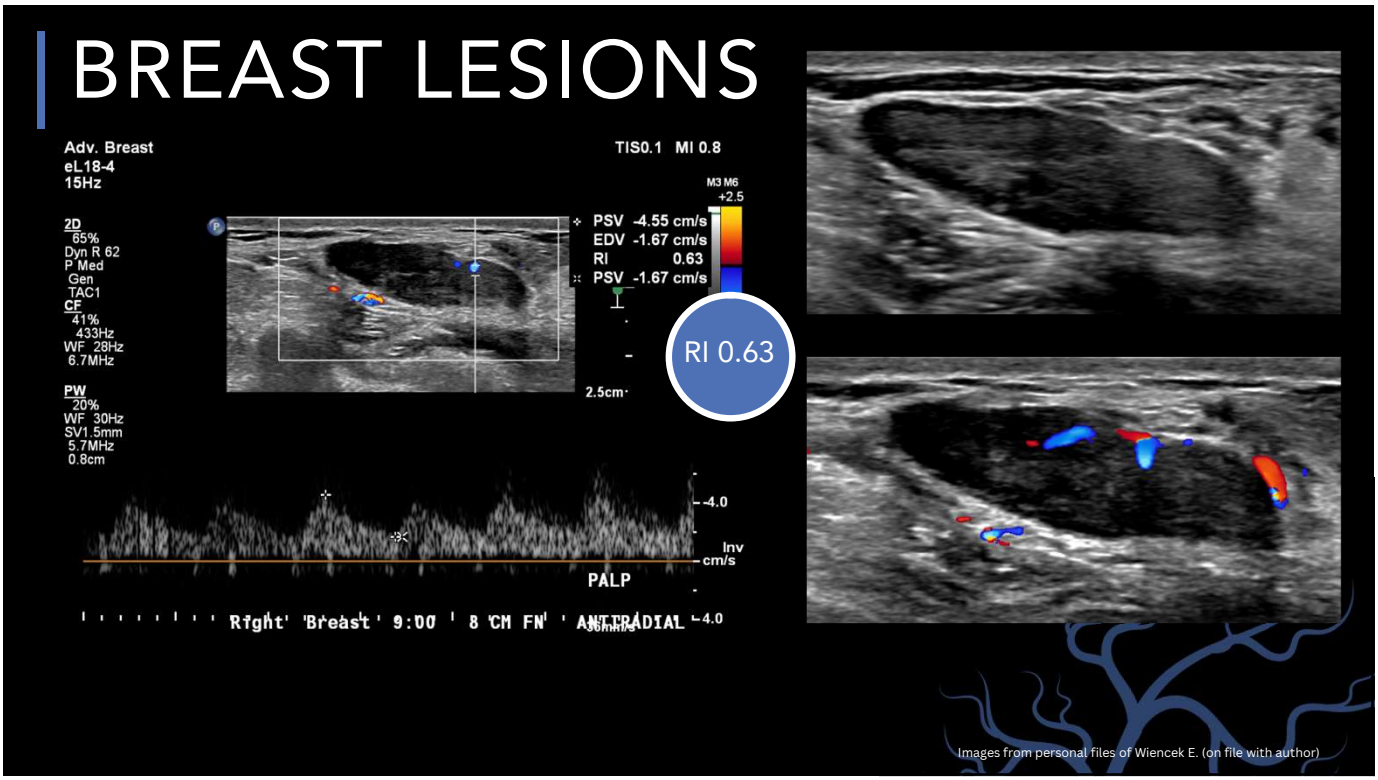
BREAST LESIONS



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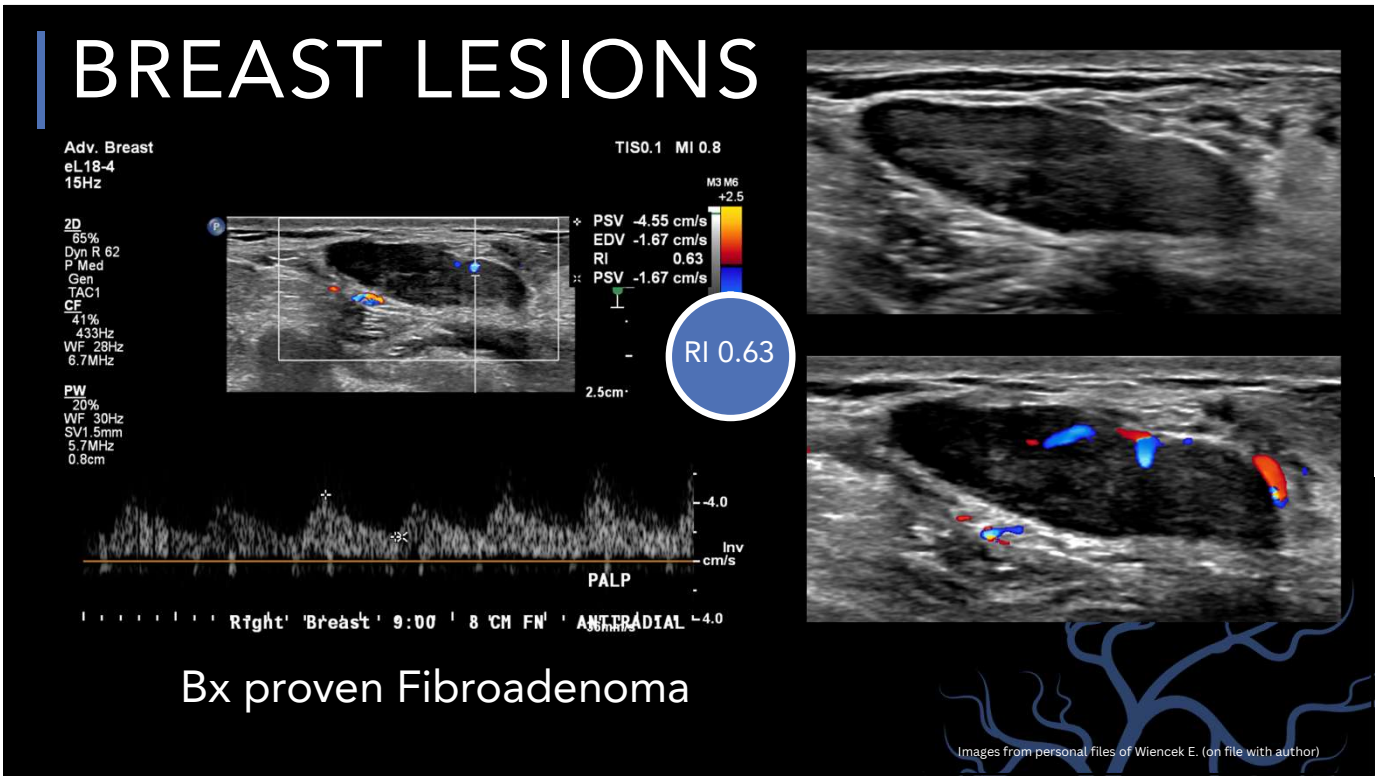
BREAST LESIONS



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6

FUTURE APPLICATIONS

- Reduce the number of biopsies
- Reduce patient anxiety
- Lower costs to patients
- Faster diagnosis & subsequent treatment

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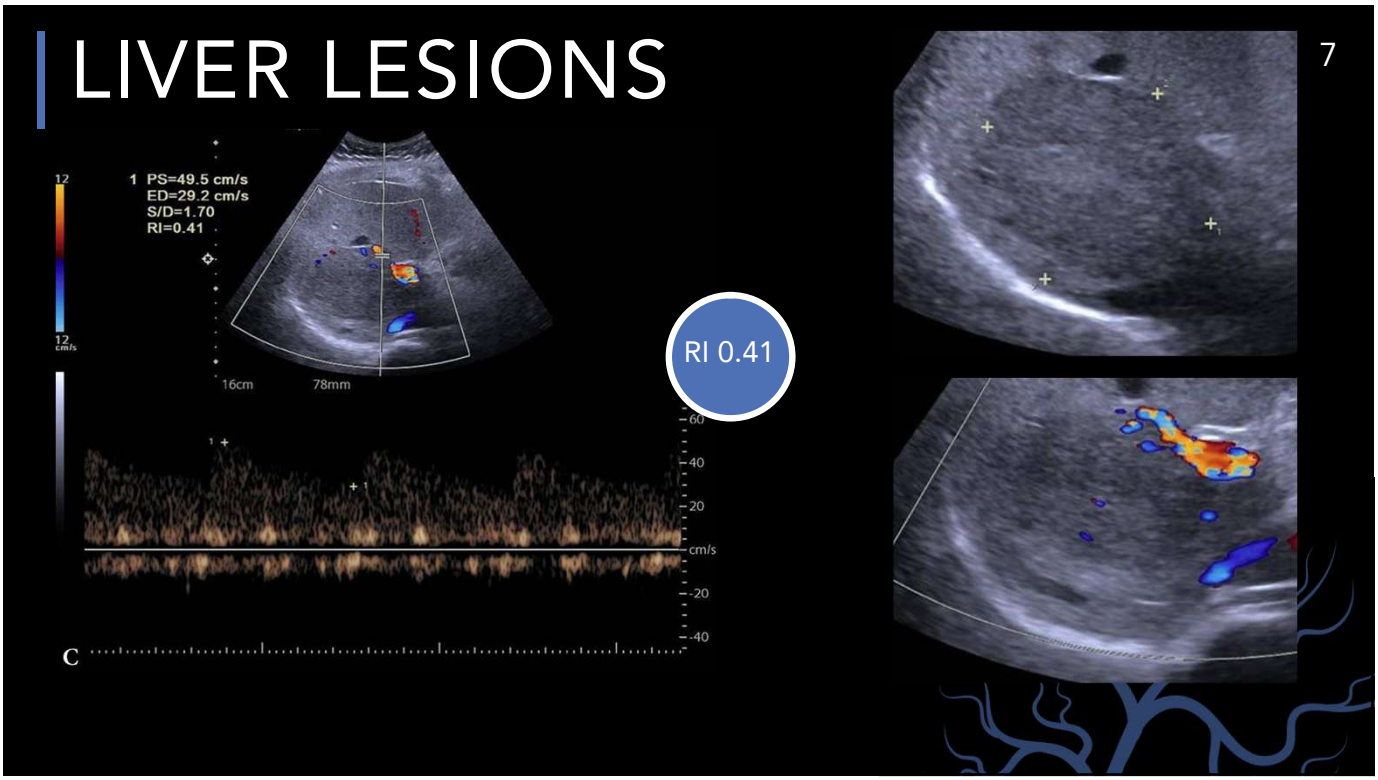
7

LIVER LESIONS

RI ≥ 0.615 indicates malignancy

sensitivity: 81%
specificity: 82%

46



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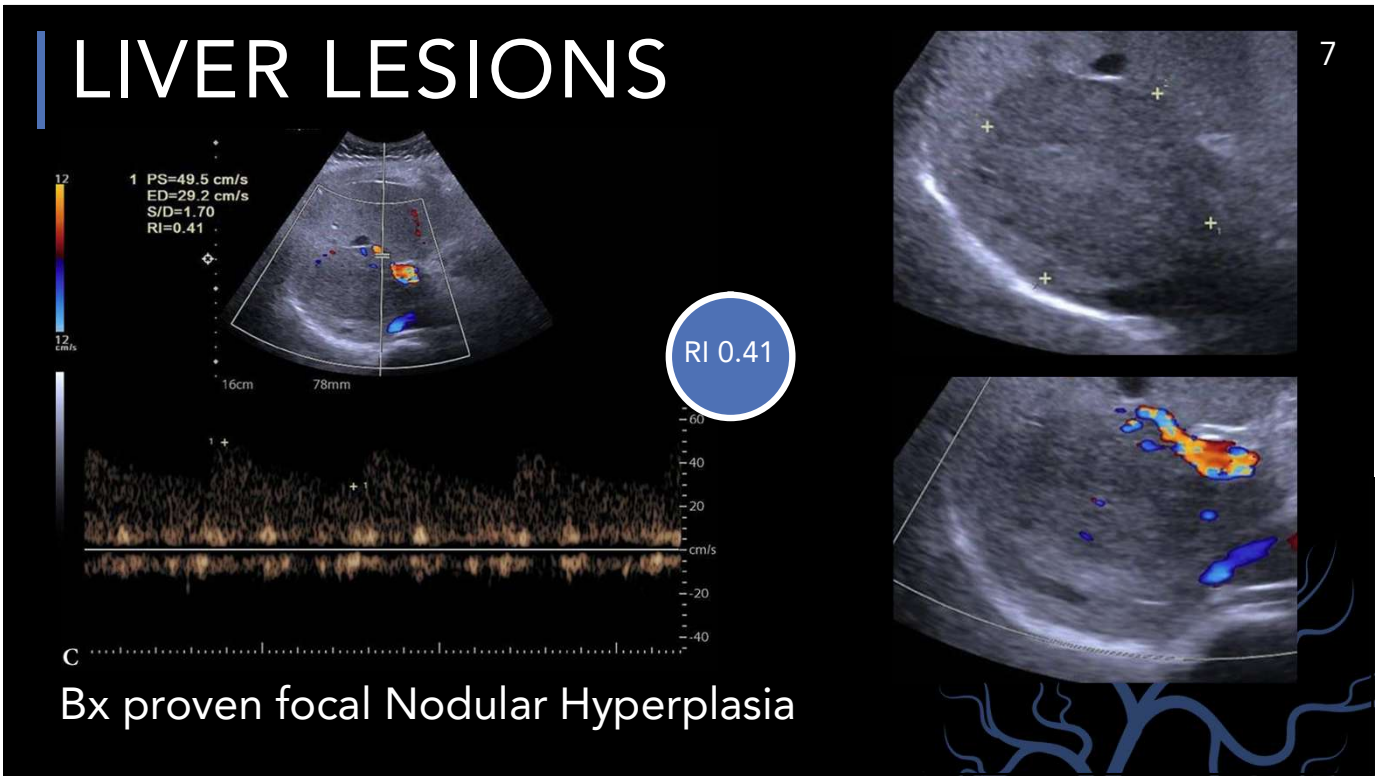

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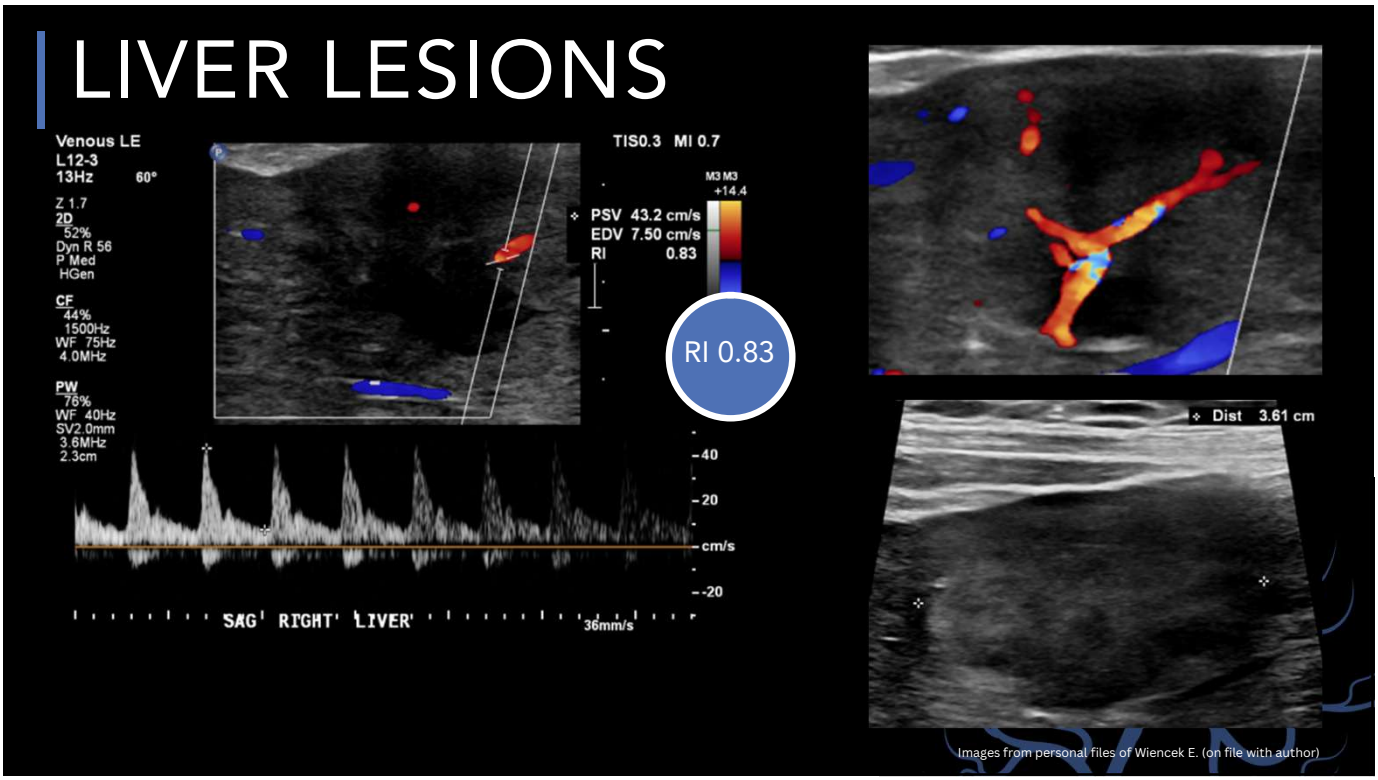

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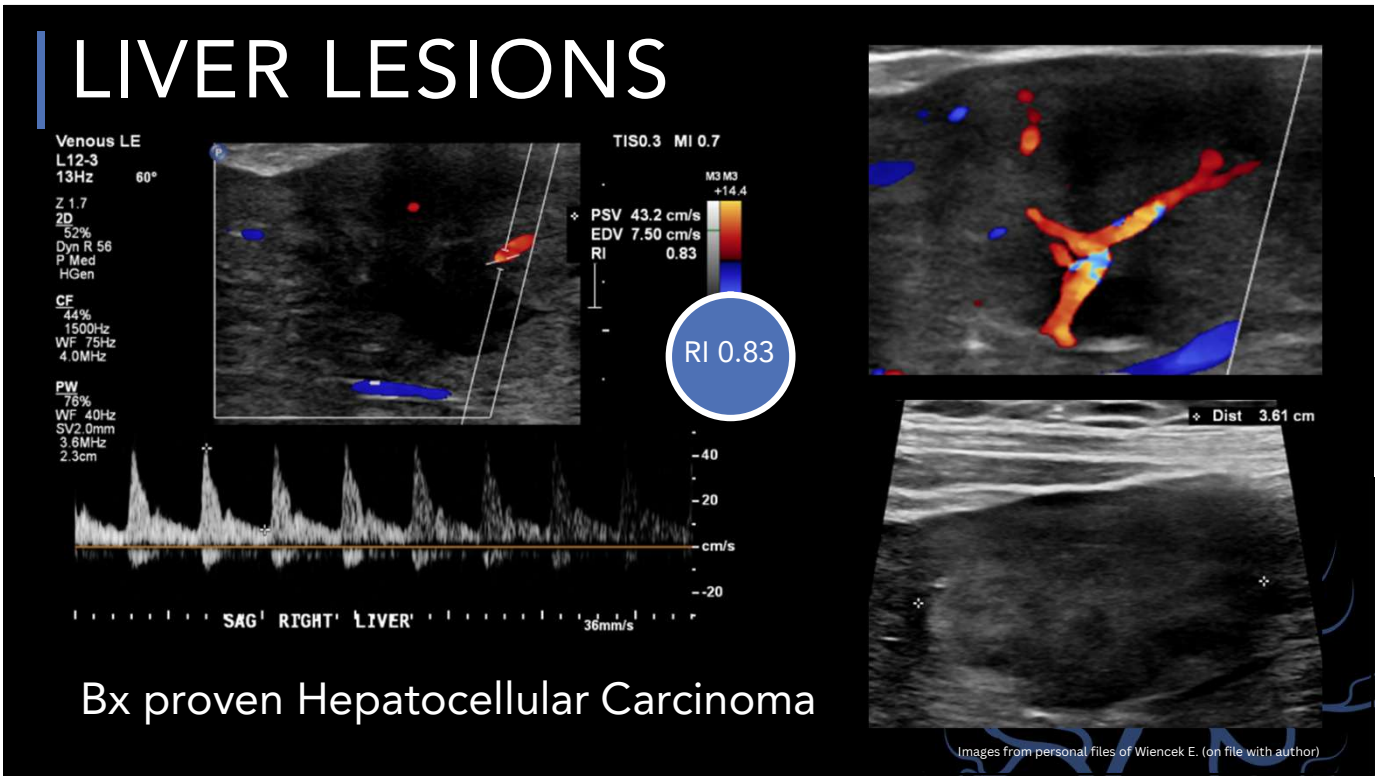

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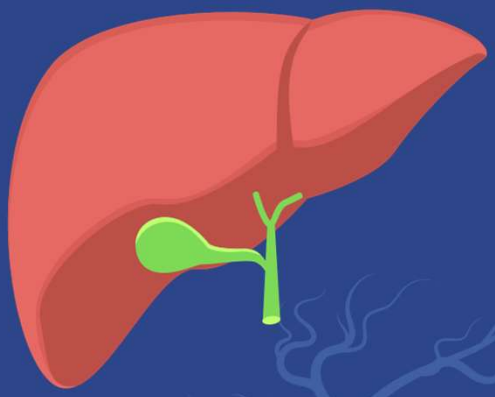
FUTURE APPLICATIONS

- RI combined with grayscale characteristics is a great tool to help differentiate benign from malignant lesions



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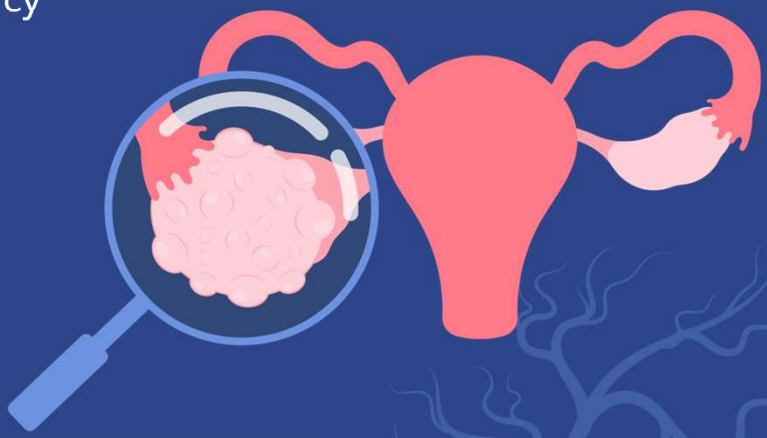
8

OVARIAN NEOPLASMS

RI≤0.45 indicates malignancy

sensitivity: 86%
specificity: 70%



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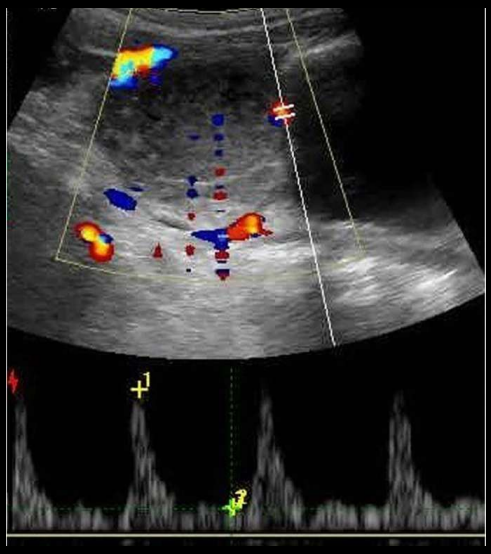
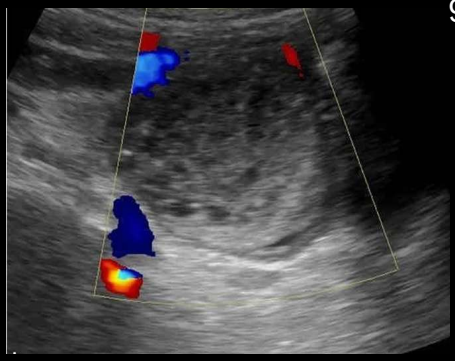
OVARIAN



RI 0.71



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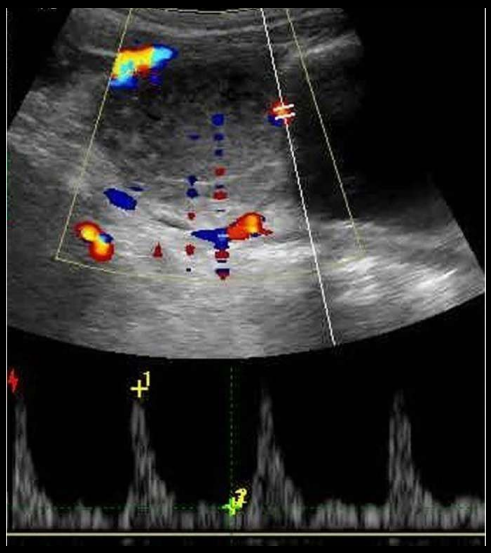
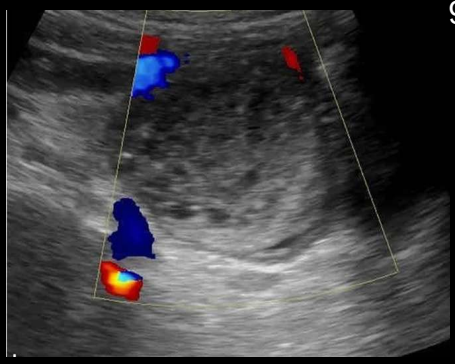
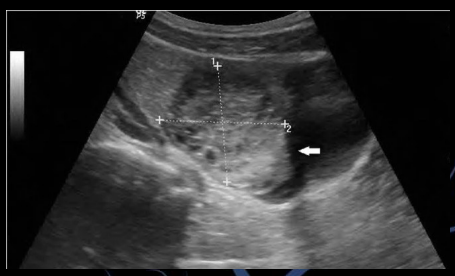
OVARIAN



RI 0.71





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Hemorrhagic Cyst

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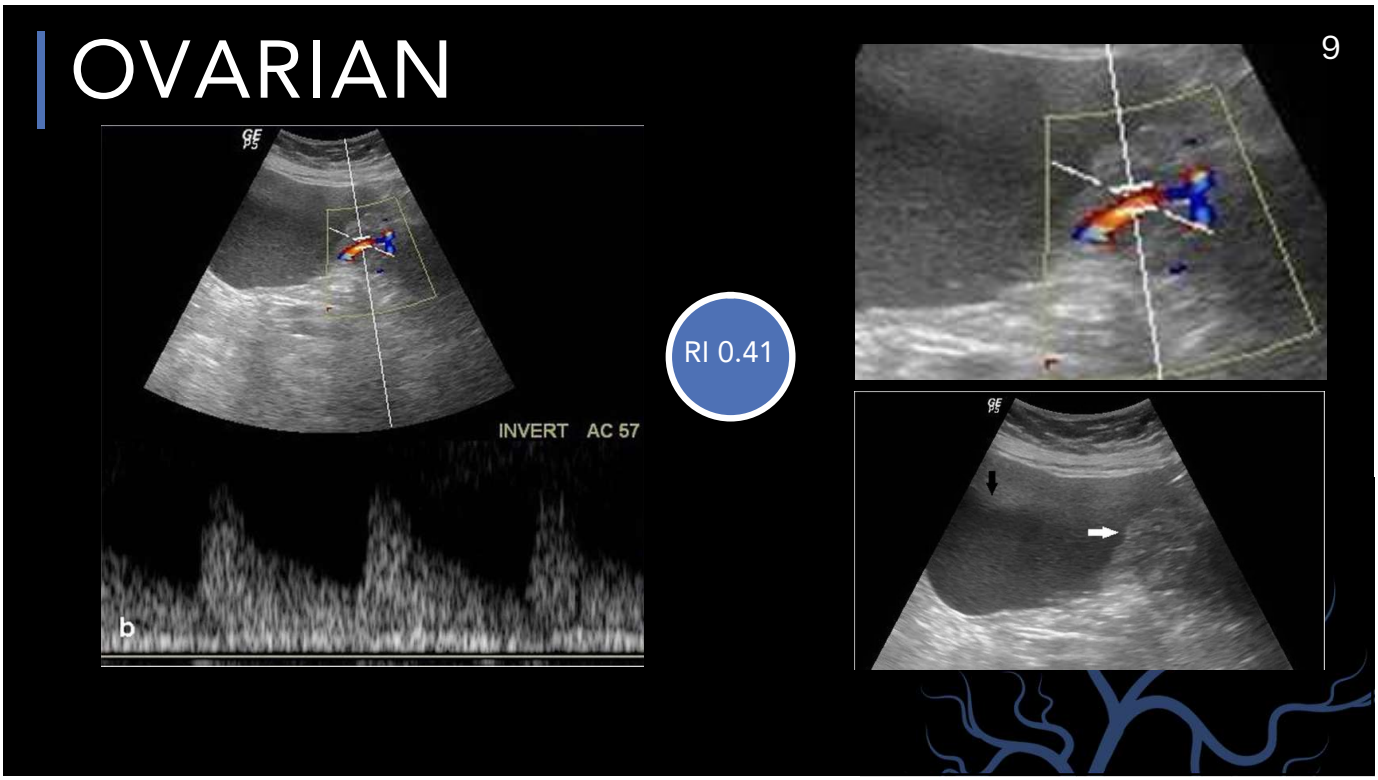

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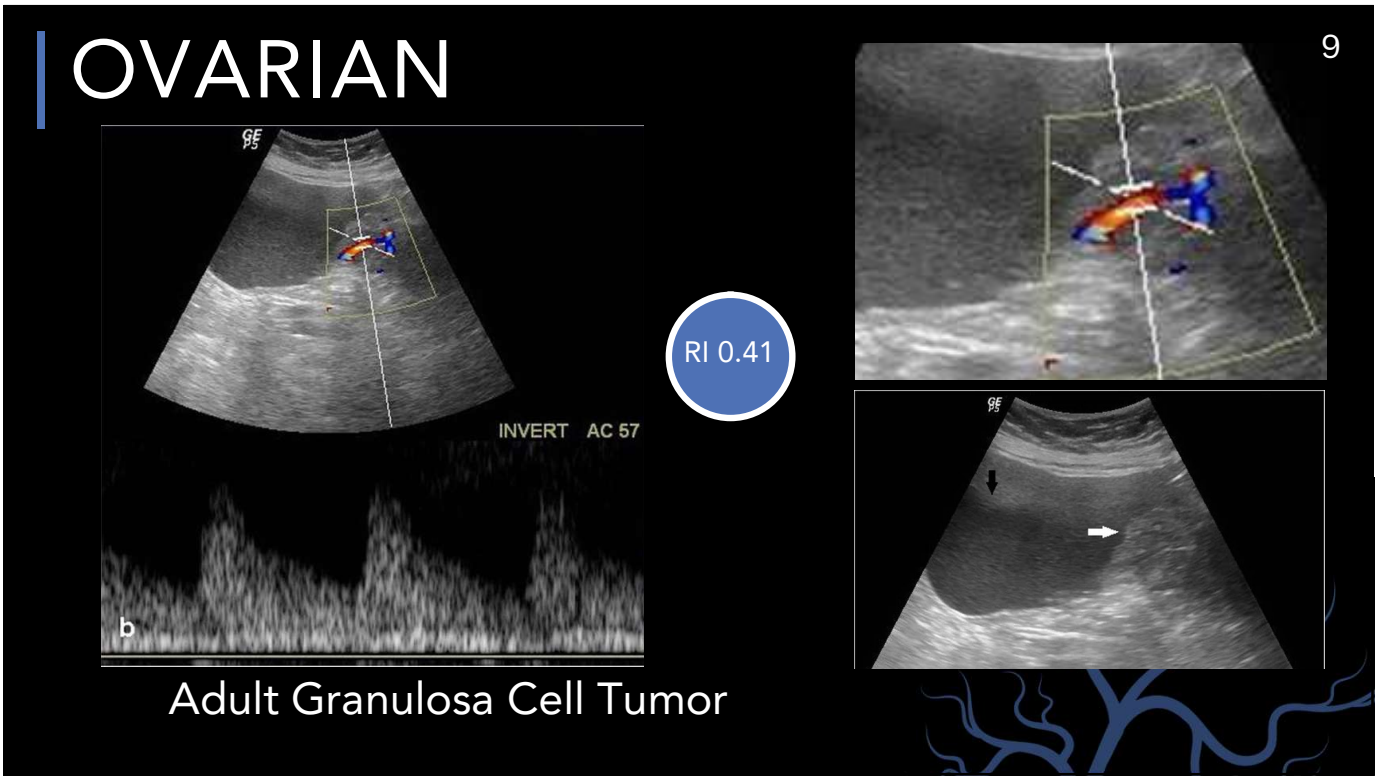

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OVARIAN NEOPLASMS

Why are ovarian neoplasms different?
Possibly attributed to:

- Ovarian malignancies tend to be "softer"
- Wide variety of cellular makeup of ovarian lesion

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OVARIAN NEOPLASMS

"This study reveals that unlike malignant lesions of other organs such as the thyroid and breast which were reported as having hard-tissue property on elastograms, tissue elasticity of ovarian malignant lesions tends to be softer"

(Herek 2016)

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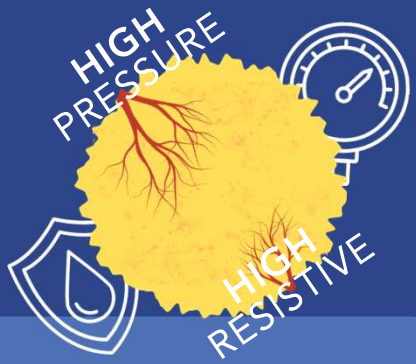
RI MIRRORS ELASTOGRAPHY

Stiffer tissues are more likely to be malignant

Recall the high pressure tumor environment that relates to high resistive index



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OVARIAN NEOPLASMS

"From our results, we reported that the color Doppler flow imaging should be used to evaluate the presence and location of flow in ovarian lesions without a need for RI or PI, as they had no more value than color flow Doppler in addition to its non-feasibility and time-consuming"

(Kalaf 2020)

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OVARIAN NEOPLASMS

- Presence of flow is more important than the characteristics of the flow
  (malignant lesions are more likely to have flow)
- Grayscale characteristics are gold standard
- Follow O-RADS!

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FUTURE IMPLICATIONS

- Why does this matter?
  - Possibility to limit number of unnecessary biopsies
  - Possibility to predict how well treatments may work on particular tumors

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BIOPSIES

Thyroid
- 5–10% of thyroid FNAs will have malignant cytology [11]
- 10–25% will be indeterminate or suspicious for cancer
- 60–70% will be benign

Lymph nodes
- 40-60% are malignant [12]

Breast
- 70–80% are negative/benign [13]

Liver
- 84% malignant [14]

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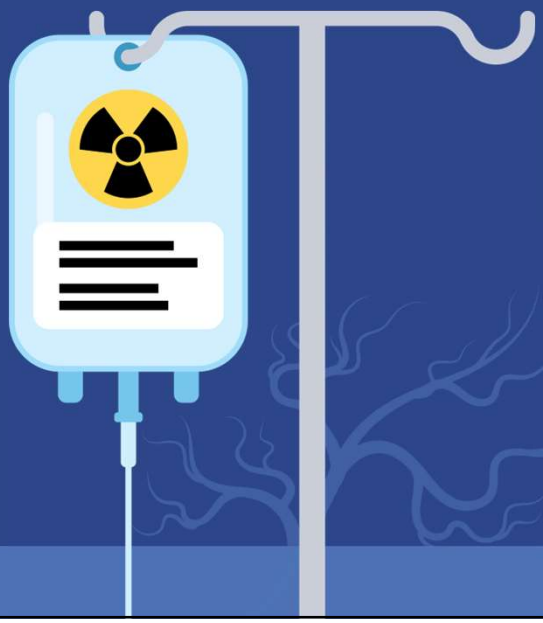
TREATMENT

- We identified a cancer
  - Now what?
- Abnormal vessels make treatment delivery to tumors difficult



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TREATMENT

- Softer tumors are more likely to respond to treatments
- Potential of ultrasound to aid in determining whether chemotherapy may be useful in a particular tumor. (More research needed)

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MODULATING THE MICROENVIRONMENT

- Therapies have been found that can improve tumor perfusion
  - Vascular normalization by blocking proangiogenic factors
  - Tumor vessel dilation

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MODULATING THE MICROENVIRONMENT

- Potential of ultrasound to determine which cancers are candidates for these therapies and track how well they are working

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ADDING SPECTRAL DOPPLER

- How do you go about this?
- How do I optimize my analysis?
  - Many lesions can be very small with very low flow

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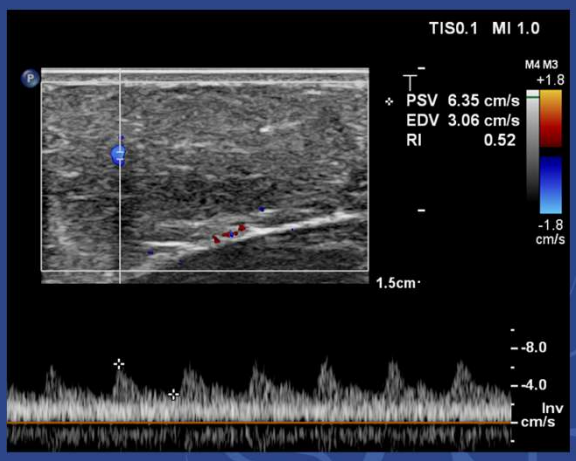
DOPPLER OPTIMIZATION

- Use a light hand/ gel standoff
- Decrease wall filter
- Decrease freq. for deep lesions
- Decrease scale to detect low flow
- Adjust spectral gate



Images from personal files of Wiencek E. (on file with author)

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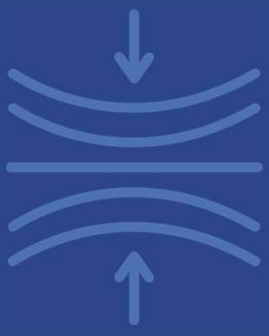
USE A LIGHT HAND/ GEL STANDOFF

- Too much pressure may compress blood vessels, making it appear as if there is no flow, especially for superficial lesions
- Too much pressure may also artificially increase velocities and resistance



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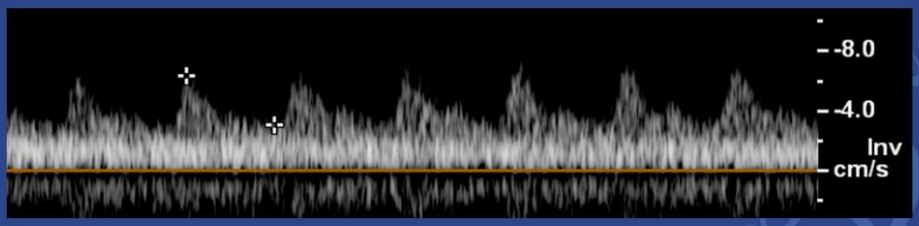
DECREASE WALL FILTER

- Wall filter removes low level echoes
- This may remove real signals in low flow states



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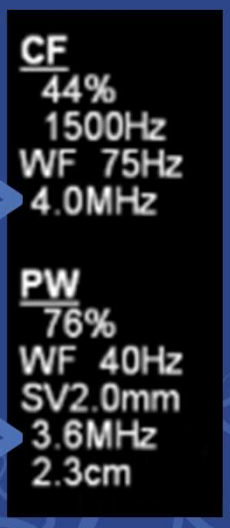
DECREASE FREQ. FOR DEEP LESIONS

- Especially useful for imaging the liver
- Can help detect and strengthen signals



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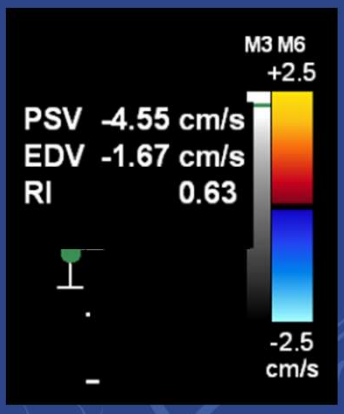
DECREASE SCALE TO DETECT LOW FLOW

- Bring down your color AND spectral scale!
- Increase gain!
- EDV is sometimes less than 2 cm/sec
- Is there no flow, or is your scale too high?



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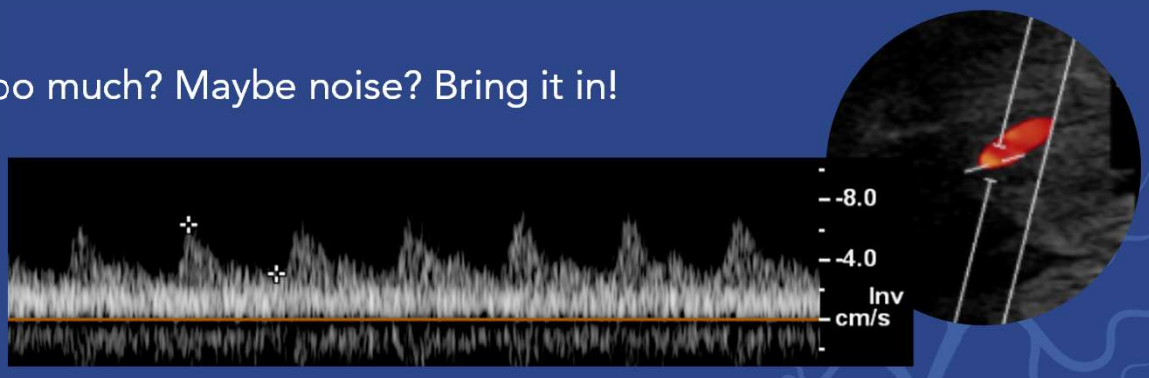
ADJUST SPECTRAL GATE

- Not getting enough information? Open the gates!
- Too much? Maybe noise? Bring it in!



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TAKE-AWAYS

- RI can be an **adjunct** in characterizing benign vs. malignant lesions of the thyroid, lymph nodes, breast, and liver
- In the future, it may prevent unneeded biopsy in lesions with indeterminate grayscale characteristics
- May be used to predict how well tumors react to treatments
- More research should be done to determine cut-off values and other applications

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Sagittal,
Transverse,
Measure It,
Put Some Color On It,
Done! < and some spectral!

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THANK YOU

Any questions?

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REFERENCES

1.Liu ZL, Chen HH, Zheng LL, Sun LP, Shi L. Angiogenic signaling pathways and anti-angiogenic therapy for cancer. Signal Transduction and Targeted Therapy. 2023;8(1). doi:https://doi.org/10.1038/s41392-023-01460-1

2.Angiogenesis Inhibitors | LUNGevity Foundation. Lungevity.org. Published 2021. https://www.lungevity.org/patients-care-partners/navigating-your-diagnosis/treatment-options/angiogenesis-inhibitors

3.Edelman SK. Understanding Ultrasound Physics. 4th ed. Esp; 2012.

4.Akhoundi N, Zahra Naseri, Alireza Siami, et al. Exploring the Diagnostic Role of Spectral Doppler as a Predictor of Malignancy Within Thyroid Nodules. Journal of diagnostic medical sonography. 2023;40(1):29-36. doi:https://doi.org/10.1177/87564793231194645

5.Gergis M, Hussein MT, Gad SF. Role of color Doppler ultrasound in differentiation between benign and malignant lymphadenopathy. Journal of Current Medical Research and Practice. 2023;8(4):165-170. doi:https://doi.org/10.4103/jcmrp.jcmrp_32_23

6.Mehdikhani B, Benam M, Moradkhani A, et al. Evaluation of diagnostic value of Doppler ultrasound in the diagnosis of malignant breast masses. European Journal of Translational Myology. Published online March 26, 2024. doi:https://doi.org/10.4081/ejtm.2024.12372

7.Dong Y, Wang WP, Ignee A, et al. The diagnostic value of Doppler Resistive Index in the differential diagnosis of focal liver lesions. Journal of Ultrasonography. 2023;23(93):45-52. doi:https://doi.org/10.15557/jou.2023.0010

8.Zhou L, Xuan Z, Yu W. Diagnostic value of ultrasound score, color Doppler ultrasound RI and spiral CT for ovarian tumors. Oncology Letters. Published online April 4, 2019. doi:https://doi.org/10.3892/ol.2019.10215

9.Khalaf LMR, Desoky HHM, Seifeldein GS, Salah A, Amine MA, Hussien MT. Sonographic and Doppler predictors of malignancy in ovarian lesions. Egyptian Journal of Radiology and Nuclear Medicine. 2020;51(1). doi:https://doi.org/10.1186/s43055-020-00172-8

10.Herek D, Aysun Karabulut, Kadir Agladioglu. Usefulness of transabdominal real-time sonoelastography in the evaluation of ovarian lesions: preliminary results. British Journal of Radiology. 2016;89(1065):20160173-20160173. doi:https://doi.org/10.1259/bjr.20160173

11.Bessey LJ, Lai NBK, Coorough NE, Chen H, Sippel RS. The incidence of thyroid cancer by f ine needle aspiration varies by age and gender. Journal of Surgical Research. 2013;184(2):761-765. doi:https://doi.org/10.1016/j.jss.2013.03.086

12.Ferrer R. Lymphadenopathy: Differential Diagnosis and Evaluation. American Family Physician. 1998;58(6):1313-1320. https://www.aafp.org/pubs/afp/issues/1998/1015/p1313.html

13.Liu C, Sun M, Dooman Arefan, Zuley M, Sumkin J, Wu S. Deep learning of mammogram images to reduce unnecessary breast biopsies: a preliminary study. Breast Cancer Research. 2024;26(1). doi:https://doi.org/10.1186/s13058-024-01830-9

14.Khalifa A, Sasso R, Rockey DC. Role of Liver Biopsy in Assessment of Radiologically Identified Liver Masses. Digestive Diseases and Sciences. 2021;67(1):337-343. doi:https://doi.org/10.1007/s10620-021-06822-9

15.Zhang B, Hu Y, Pang Z. Modulating the Tumor Microenvironment to Enhance Tumor Nanomedicine Delivery. Frontiers in Pharmacology. 2017;8. doi:https://doi.org/10.3389/fphar.2017.00952

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