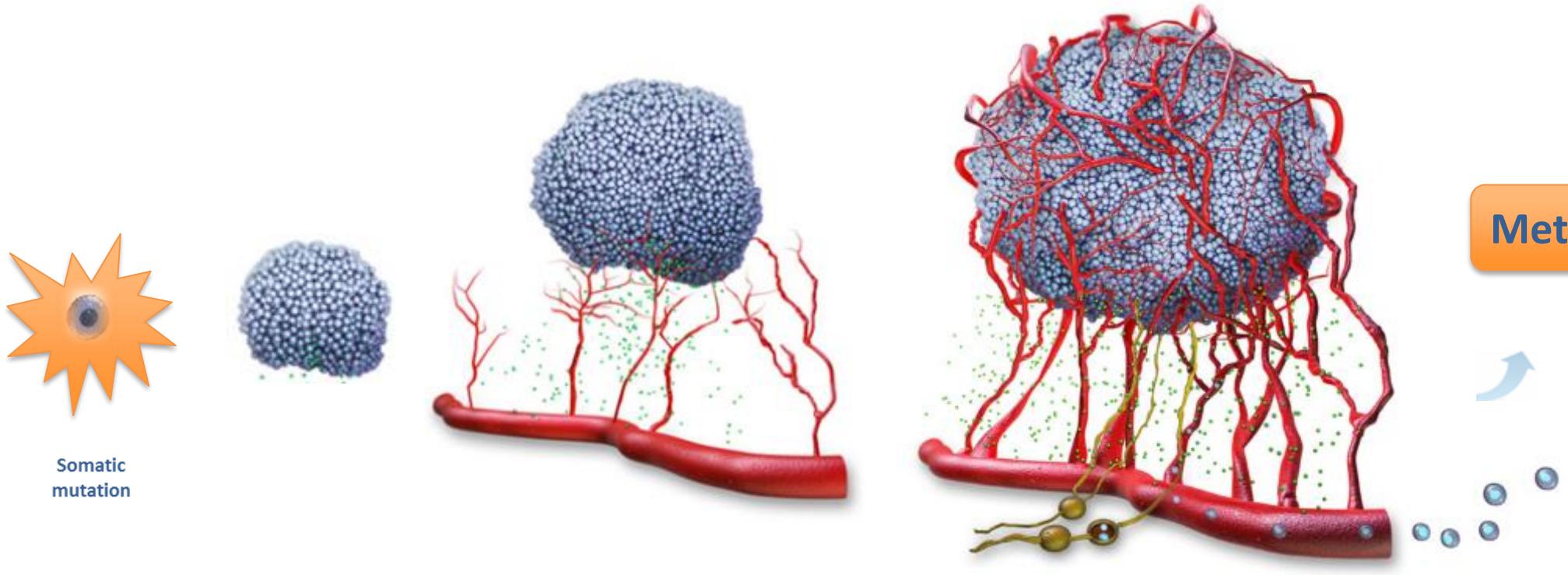
Optoacoustic imaging is helpful in predicting breast cancer molecular subtypes

B. Dogan, G. Menezes, R. Butler, E. Neuschler, P. Lavin, R. Aitchison, L.F. Tucker, P. Otto, S. Grobmyer;

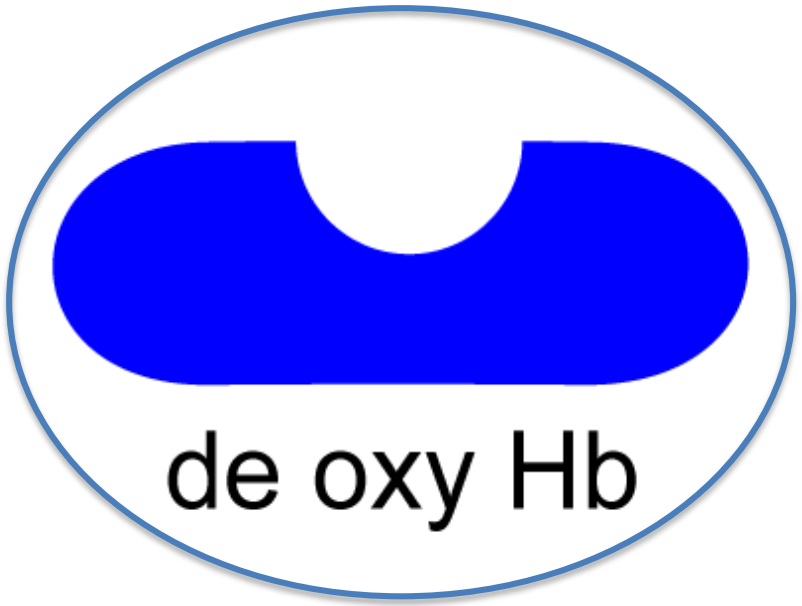
Conflicts of interest

- **B. Dogan:** None. **G. Menezes:** Employee; Part-time employment contract at Seno Medical Instruments. **R. Butler:** None. **E. Neuschler:** None. **P. Lavin:** Consultant; Research contract with Seno Medical Instruments to provide study design and analysis services.**R. Aitchison:** Consultant; Research contract with Seno Medical Instruments to provide study design and analysis services. **L.F. Tucker:** None. **P. Otto:** None. **S. Grobmyer:** Advisory Board; Member of the Medical Advisory Board at Seno Medical Instruments.

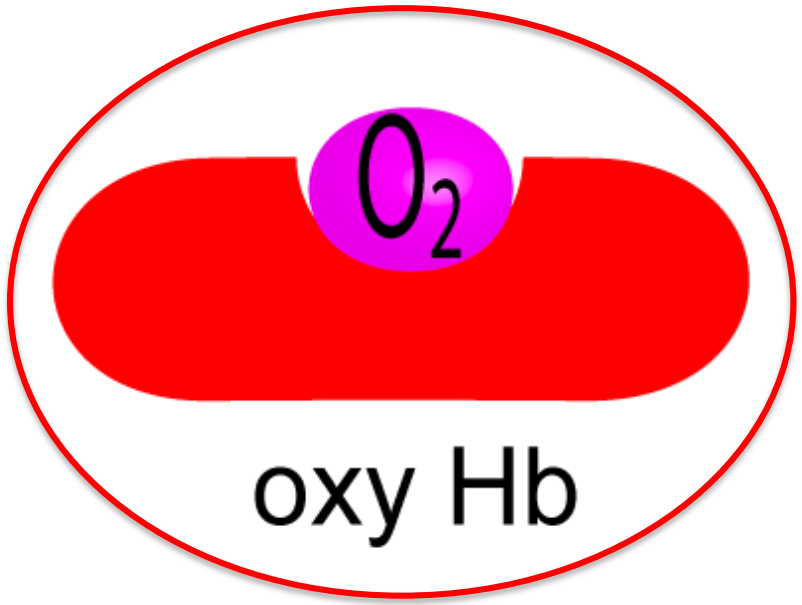
Angiogenesis



How does Optoacoustic (OA) work?

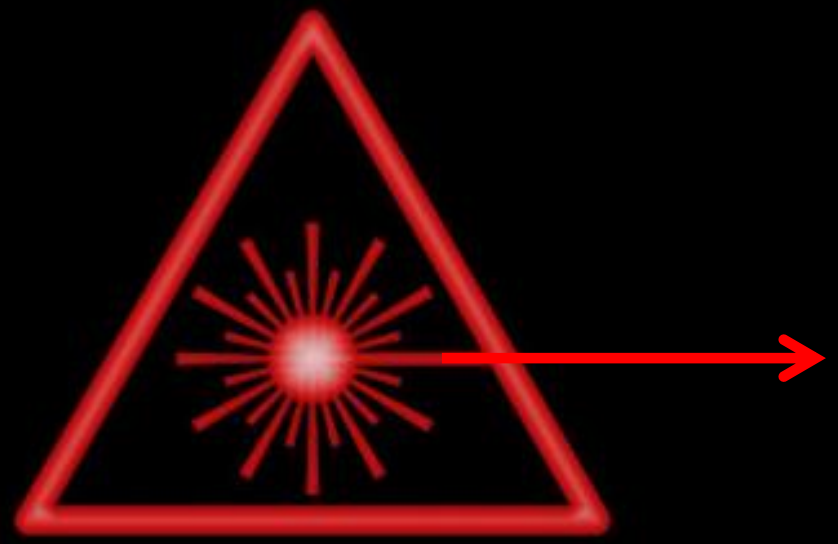


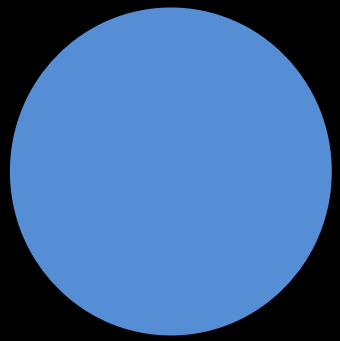
Malignant

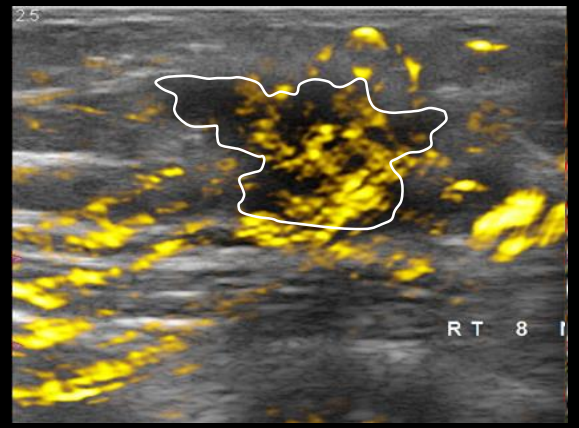


Benign

How does Optoacoustic (OA) work?







D

O

Aim of the study

- To investigate the potential role of OA/US (Optoacoustic combined with US) in non-invasively diagnosing breast cancer molecular subtypes.

Methods

- Prospective, multicenter, observational study.
- We analyzed the data retrospectively to determine the relationship between OA/US and breast cancer molecular subtypes.
- Analysis of OA/US features and tumor molecular subtypes of LUMA, LUMB, TNBC and HER2-E was performed using ANOVA, Kruskal Wallis and Wilcoxon-Mann tests.

Results

- 1690 patients with 1757 breast masses were included in this study (between 2012 and 2015).
- All masses underwent histopathological analysis.
- 1079 masses were benign and 678 were malignant.
- From these 678, 532 masses with available molecular subtypes were included in the study.
- 186 (35%) LUMA, 244 (46%) LUMB, 79 (15%) TNBCs and 23 (4%) HER2-E.
- Seven blinded readers scored the Internal and External OA/US features of identified cancers.

US and OA Scoring Systems

Internal Features

	US Shape Scores
0	Ovoid, parallel orientation, (wider than tall), >2/1 ratio max width to AP dimension
1	Ovoid, parallel orientation, (wider than tall), < 2/1 ratio width to AP
2	Round
3	Irregular without angles
4	Irregular, non-parallel orientation, (taller than wide), with or without angles
5	Irregular with angles

	US Internal Texture
0	Homogeneous hyperechoic
1	Complex mixed cystic and solid
2	Homogeneous isoechoic or mildly hypoechoic
3	Heterogeneous
4	Heterogeneous with internal microcalcifications
5	Homogeneous severely hypoechoic

	US Sound Transmission Scores
0	Enhanced
1	Normal
2	Mixed normal and enhanced
3	Mixed enhanced and partial shadowing
4	Partial shadowing
5	Complete shadowing

External Features

	US Boundary Zone Scores
0	Well-circumscribed with complete thin hyperechoic capsule
1	Well-circumscribed with partial thin hyperechoic capsule
2	Thick well-defined capsule
3	Well-circumscribed, but without thin hyperechoic capsule
4	Indistinct margin
5	Thick ill-defined halo in boundary zone
6	Frank hypoechoic and/or hyperechoic spiculations within boundary zone

	US Peripheral Zone Scores
0	Normal tissue
1	Critical angle phenomena
2	Surrounding ducts affected (duct extension or branch pattern)
3	Surrounding affected ducts containing microcalcifications
4	Peripheral long hyperechoic spicules

Internal Features

	OA/US Internal Vascularity and Deoxygenation (Vessel Score)
0	No internal vessels
1	Normal internal vessels without branches, red or green
2	Normal internal vessels with branches, mostly green
3	Internal speckle; green = red in amount and less red than background
4	Internal speckle or signal; red > green and red > background
5	Multiple internal red vessels

	OA/US Internal Tumor Blush and Deoxygenation (Blush Score)
0	No internal vessels
1	Minimal internal speckle, all green
2	Mild internal speckle; red=green and red + green < background
3	Mild internal speckle; red > green and both < background
4	Moderate internal speckle; red > green and red also > background
5	Red blush almost fills lesion

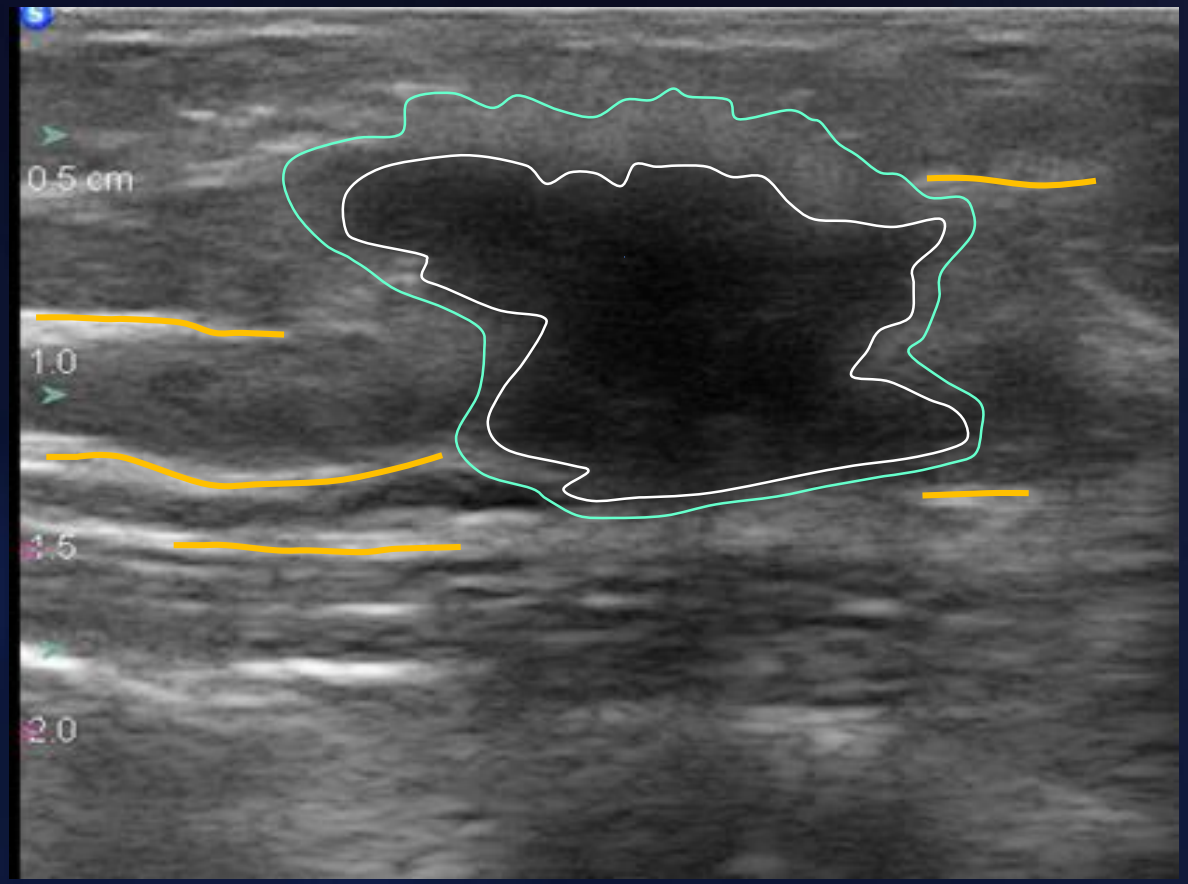
	OA/US Relative Internal Hemoglobin (Hemoglobin [Hgb] Score)
0	No internal hemoglobin (Hgb)
1	Minimal internal Hgb, less Hgb than background
2	Minimal internal Hgb in discrete vessels, Hgb = background
3	Moderate internal Hgb in discrete vessels, Hgb = background
4	Many large internal vessels containing Hgb amount > background
5	Many large Hgb filled vessels almost fill central nidus of mass

External Features

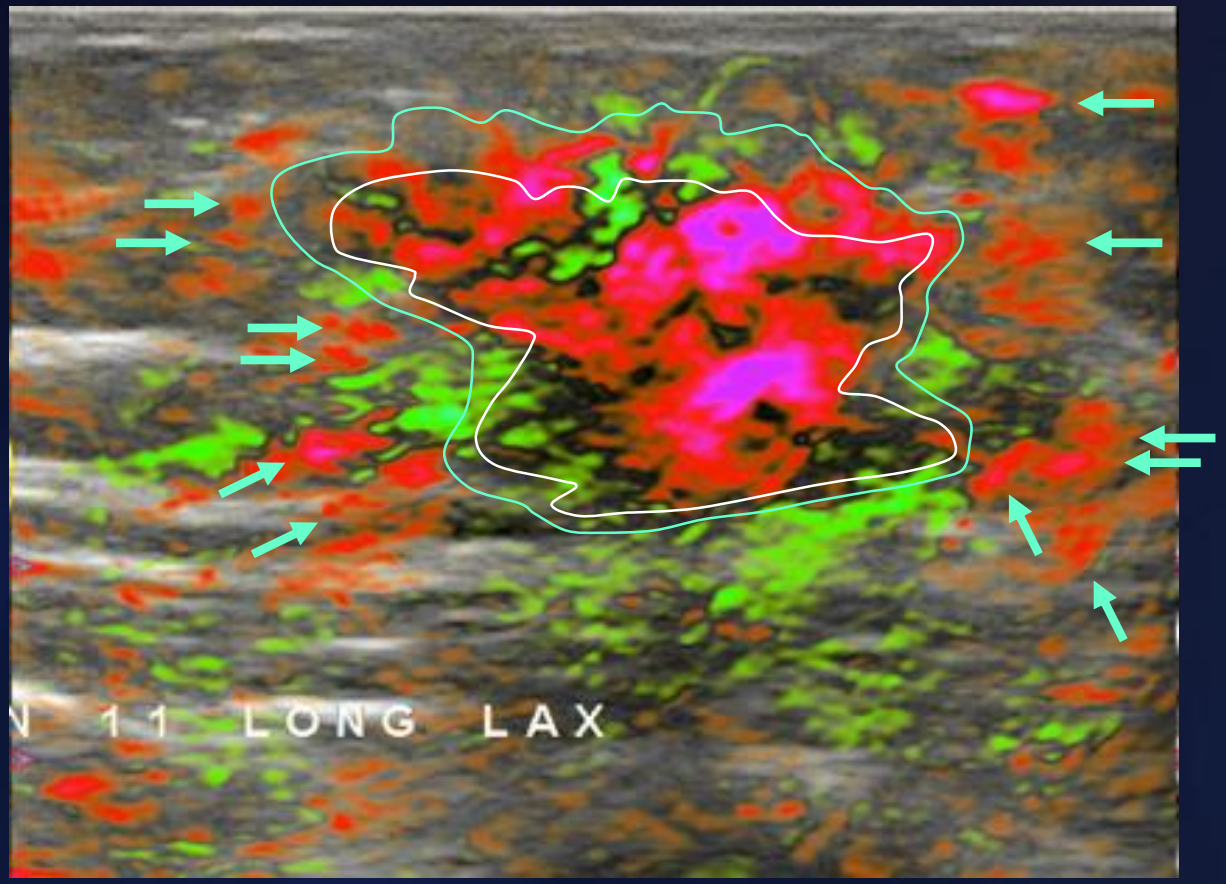
	OA/US External Boundary Zone (BZ) Vascularity and Deoxygenation (BZ Score)
0	No capsular/BZ vessels
1	Normal capsular/ BZ vessel(s) without branches (long, curved, parallel to capsule, not perpendicular to capsule)
2	Normal capsular/ BZ vessel(s) with normal tapering acutely angled branches, mostly green
3	Capsular/ BZ speckle; green = red; red < background red
4	Capsular/ BZ speckle; red > green; red > background red
5	≥3 capsular/ BZ red vessels, some perpendicular
6	Boundary zone deoxygenated blush (complete or partial)

	OA/US Peripheral Zone Radiating Vessels Score (Peripheral Zone Score)
0	No peripheral zone peri-tumoral vessels
1	1 or 2 peripheral zone feeding or draining vessels, at least one green, not in a radiating pattern
2	> 2 peripheral zone vessels, but random orientation, not radiating perpendicular to the surface of the mass
3	1 or 2 peripheral zone radiating vessels
4	> 2 peripheral zone radiating vessels on one side of the mass

US Scoring System – Internal and External Features



OA/US Scoring System – Internal and External Features



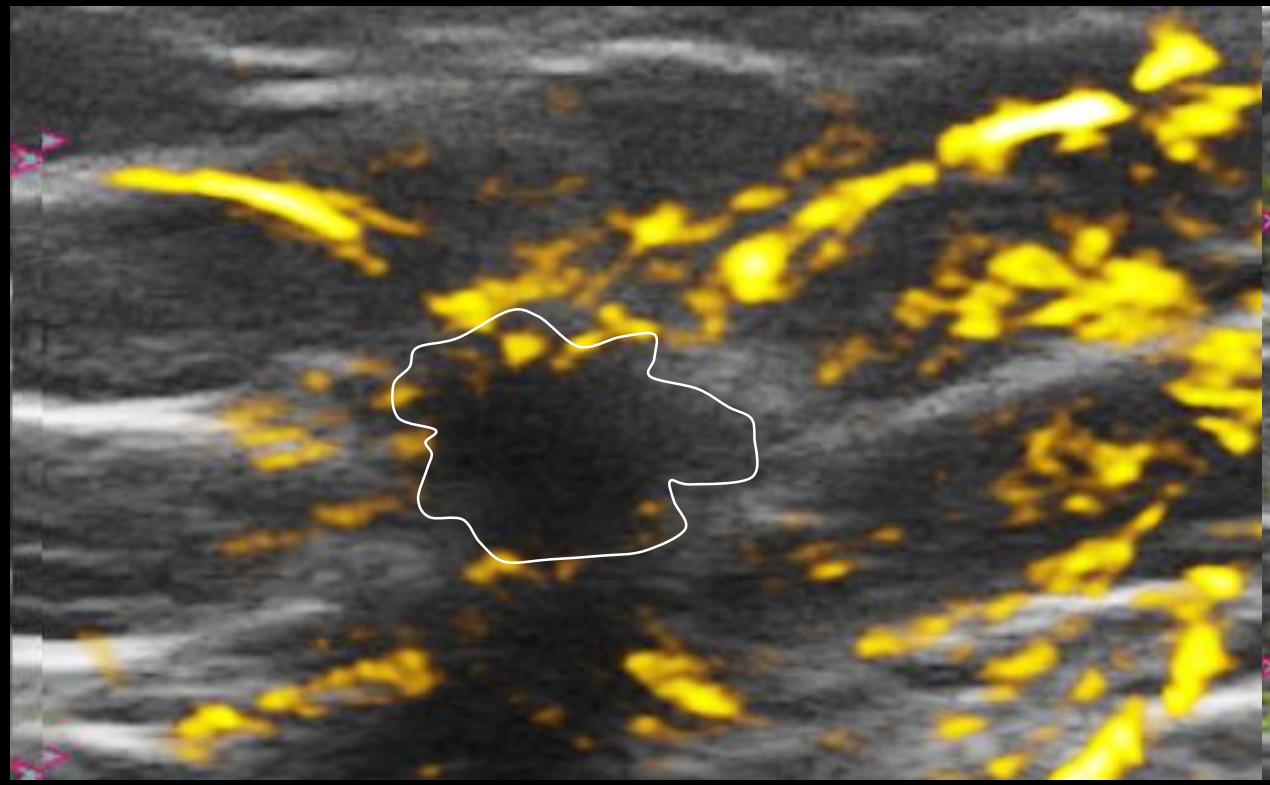
Results OA/US - Molecular Subtypes

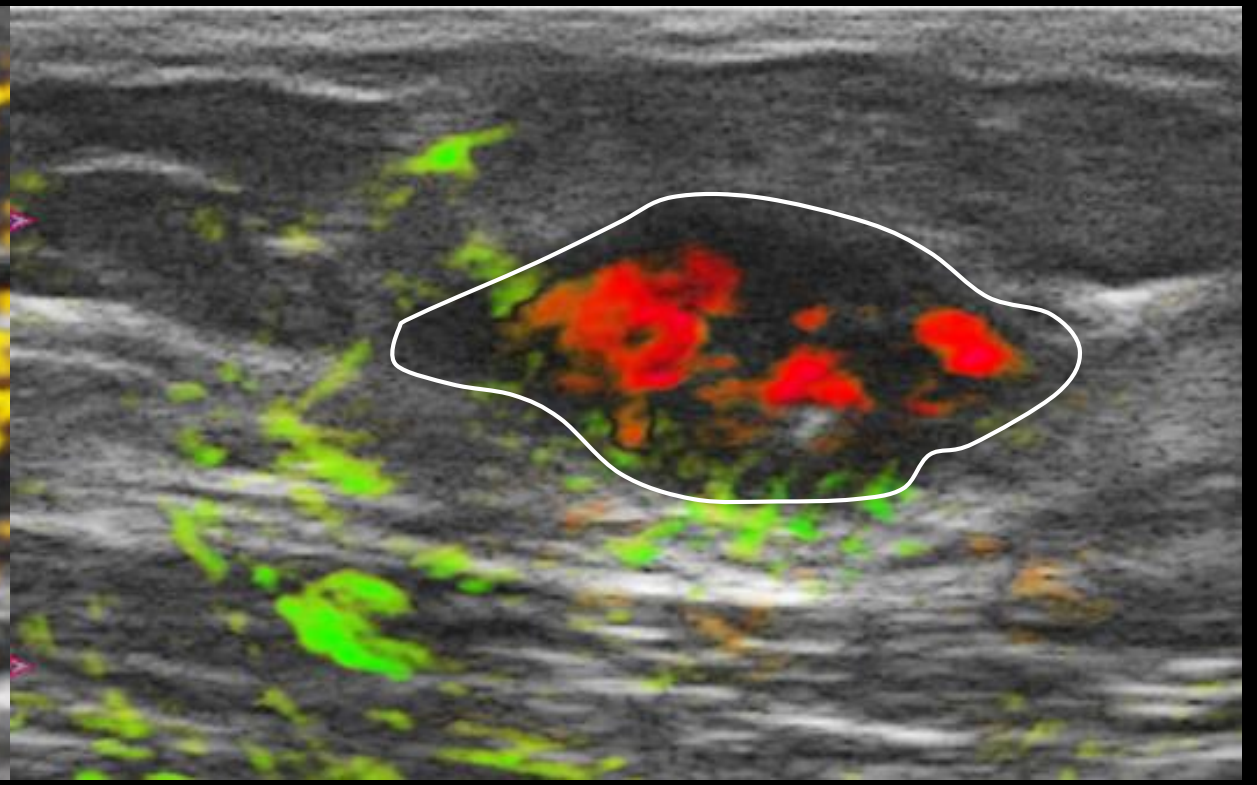
Molecular Subtypes	LUMA vs. LUMB p-values	LUMA vs TNBC p-values	LUMA vs. HER2-E p-values	LUMB vs. TNBC p-values	LUMB vs. HER2-E p-values	TNBC vs. HER2-E p-values
IUS and OA Scores Combined	1.6062×10^{-7}	1.5435×10^{-18}	3.2953×10^{-7}	2.7366×10^{-9}	0.003160	0.193116
US Sound and OA	8.4689×10^{-9}	1.1563×10^{-18}	0.000001	1.7741×10^{-8}	0.011655	0.198652
US Sound/BZ and OA	1.8434×10^{-8}	6.0246×10^{-19}	1.6953×10^{-7}	1.1369×10^{-8}	0.006252	0.260493
US Sound/Sum US Int and OA	3.6214×10^{-9}	5.7902×10^{-17}	9.5325×10^{-7}	2.7895×10^{-7}	0.006868	0.393699
US Sound/Sum US Ext and OA	9.3776×10^{-9}	2.0586×10^{-18}	2.4624×10^{-7}	2.6041×10^{-8}	0.005078	0.281403
US Sound/Sum Int and Ext and OA	1.6062×10^{-7}	1.5435×10^{-18}	3.2953×10^{-7}	2.7366×10^{-9}	0.003160	0.193116

Results OA/US - Molecular Subtypes

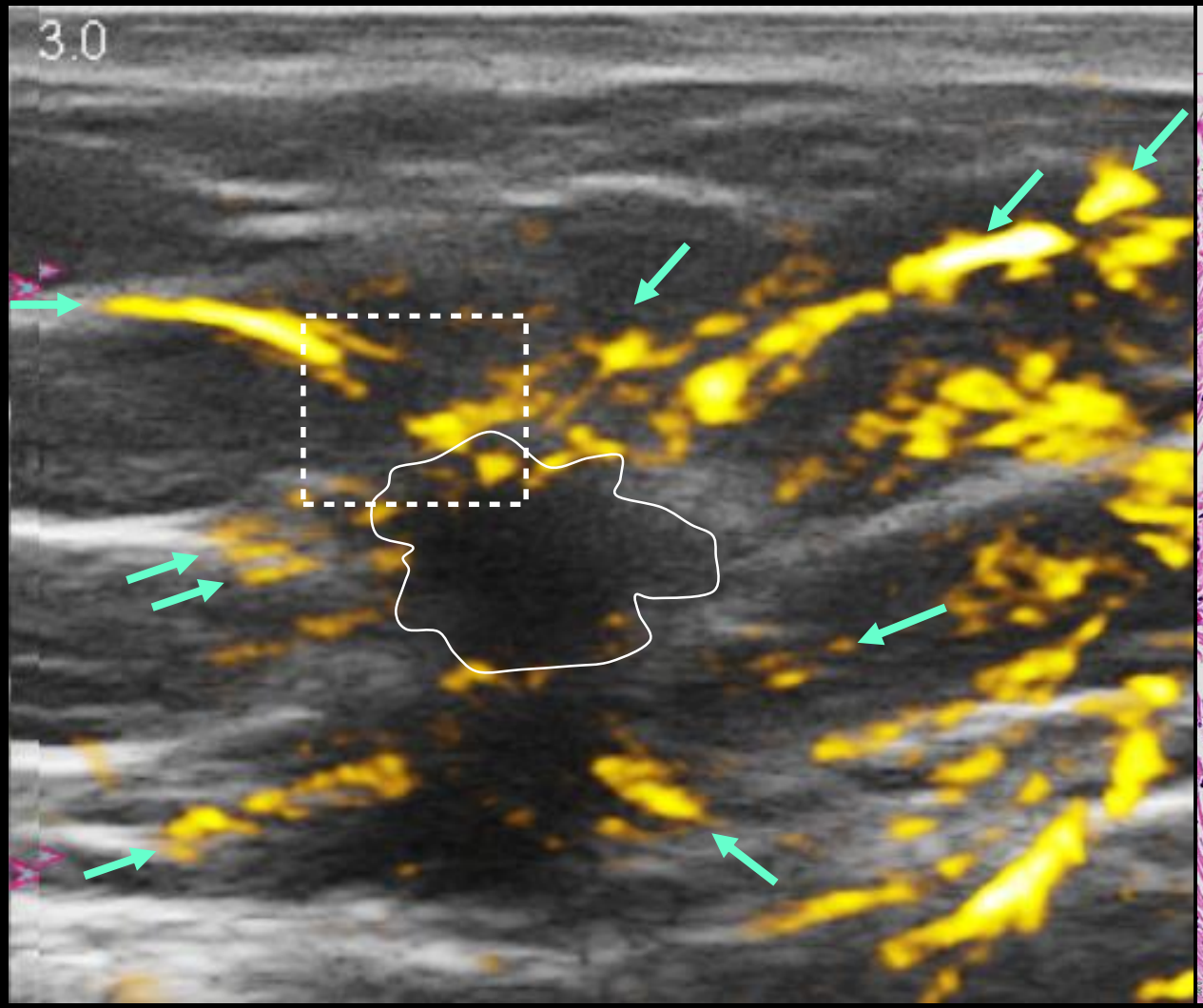
Molecular Subtypes	LUMA vs. LUMB p-values	LUMA vs TNBC p-values	LUMA vs. HER2-E p-values	LUMB vs. TNBC p-values	LUMB vs. HER2-E p-values	TNBC vs. HER2-E p-values
IUS and OA Scores Combined	1.6062×10^{-7}	1.5435×10^{-18}	3.2953×10^{-7}	2.7366×10^{-9}	0.003160	0.193116
US Sound and OA	8.4689×10^{-9}	1.1563×10^{-18}	0.000001	1.7741×10^{-8}	0.011655	0.198652
US Sound/BZ and OA	1.8434×10^{-8}	6.0246×10^{-19}	1.6953×10^{-7}	1.1369×10^{-8}	0.006252	0.260493
US Sound/Sum US Int and OA	3.6214×10^{-9}	5.7902×10^{-17}	9.5325×10^{-7}	2.7895×10^{-7}	0.006868	0.393699
US Sound/Sum US Ext and OA	9.3776×10^{-9}	2.0586×10^{-18}	2.4624×10^{-7}	2.6041×10^{-8}	0.005078	0.281403
US Sound/Sum Int and Ext and OA	$p = 1.6062 \times 10^{-7}$	$p = 1.5435 \times 10^{-18}$	3.2953×10^{-7}	2.7366×10^{-9}	0.003160	0.193116

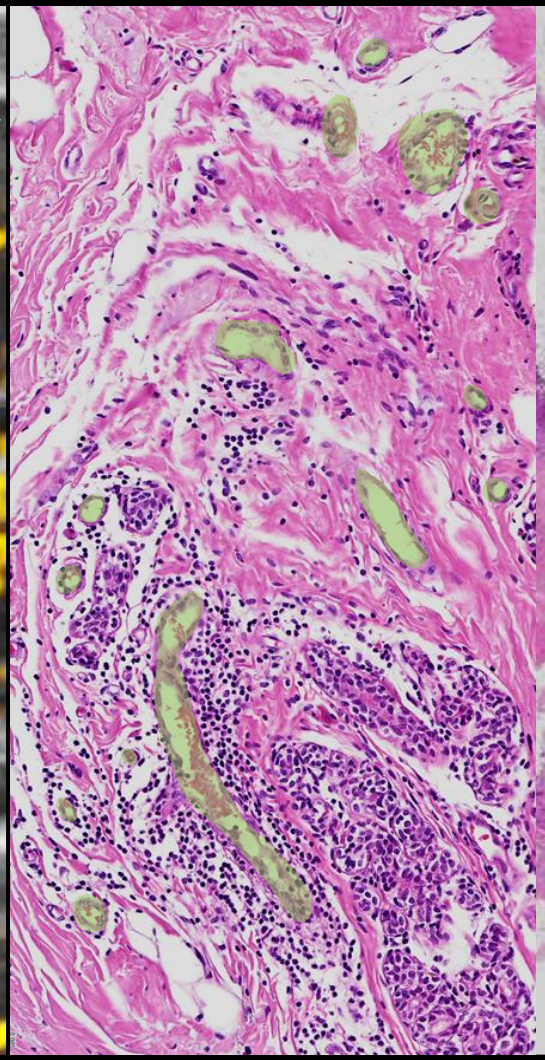
LUMA vs. TNBC

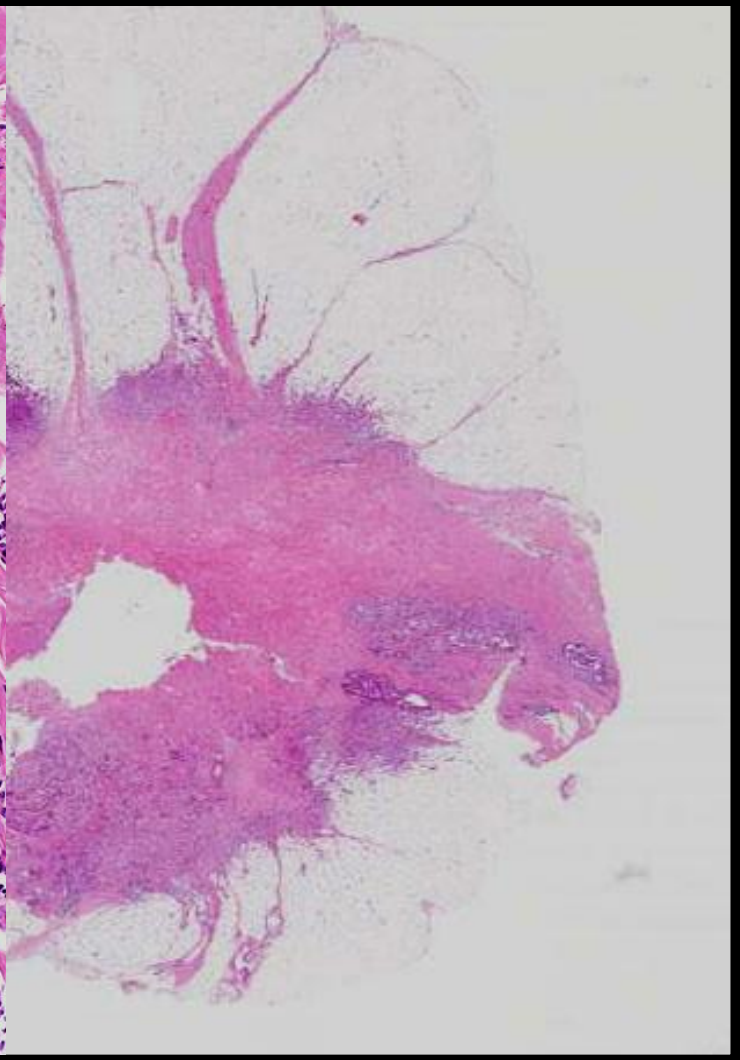




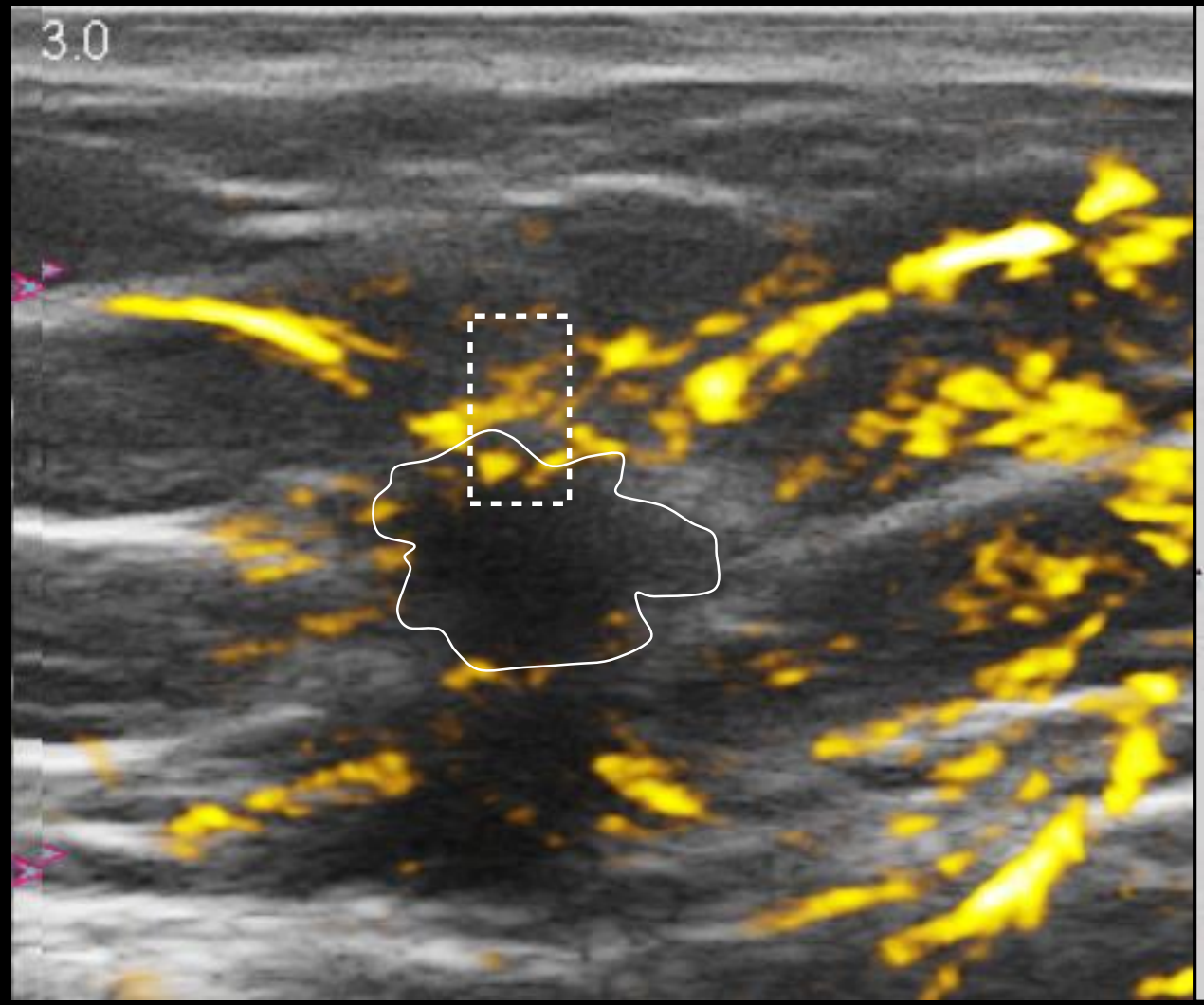
LUMA – Predominantly External Findings

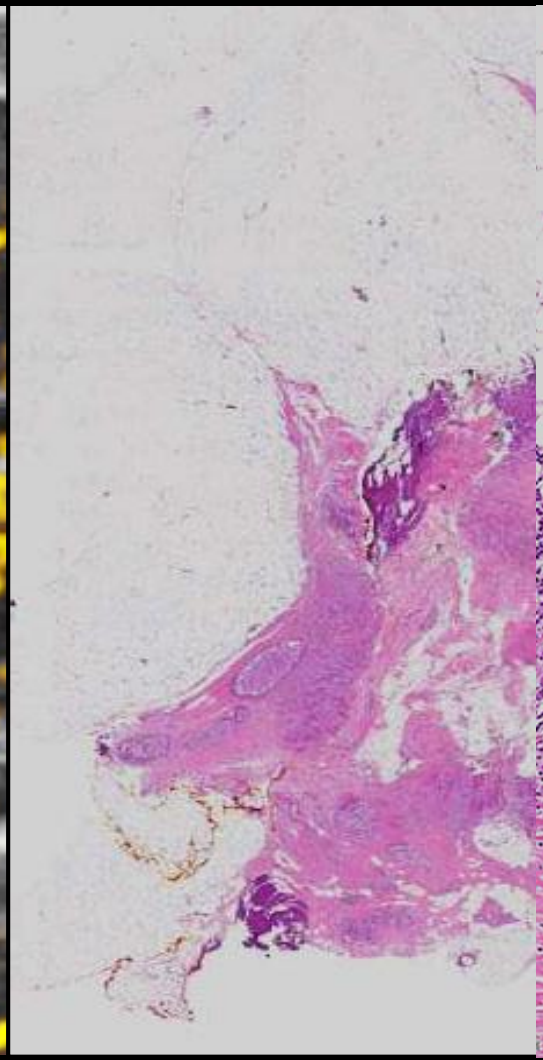


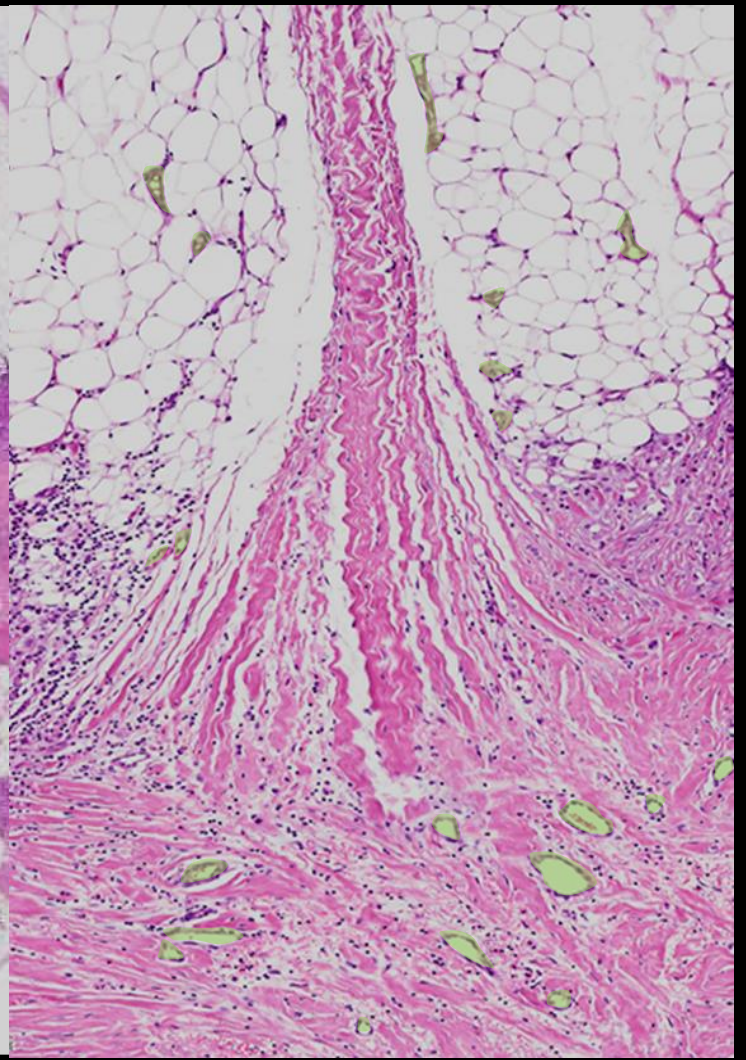




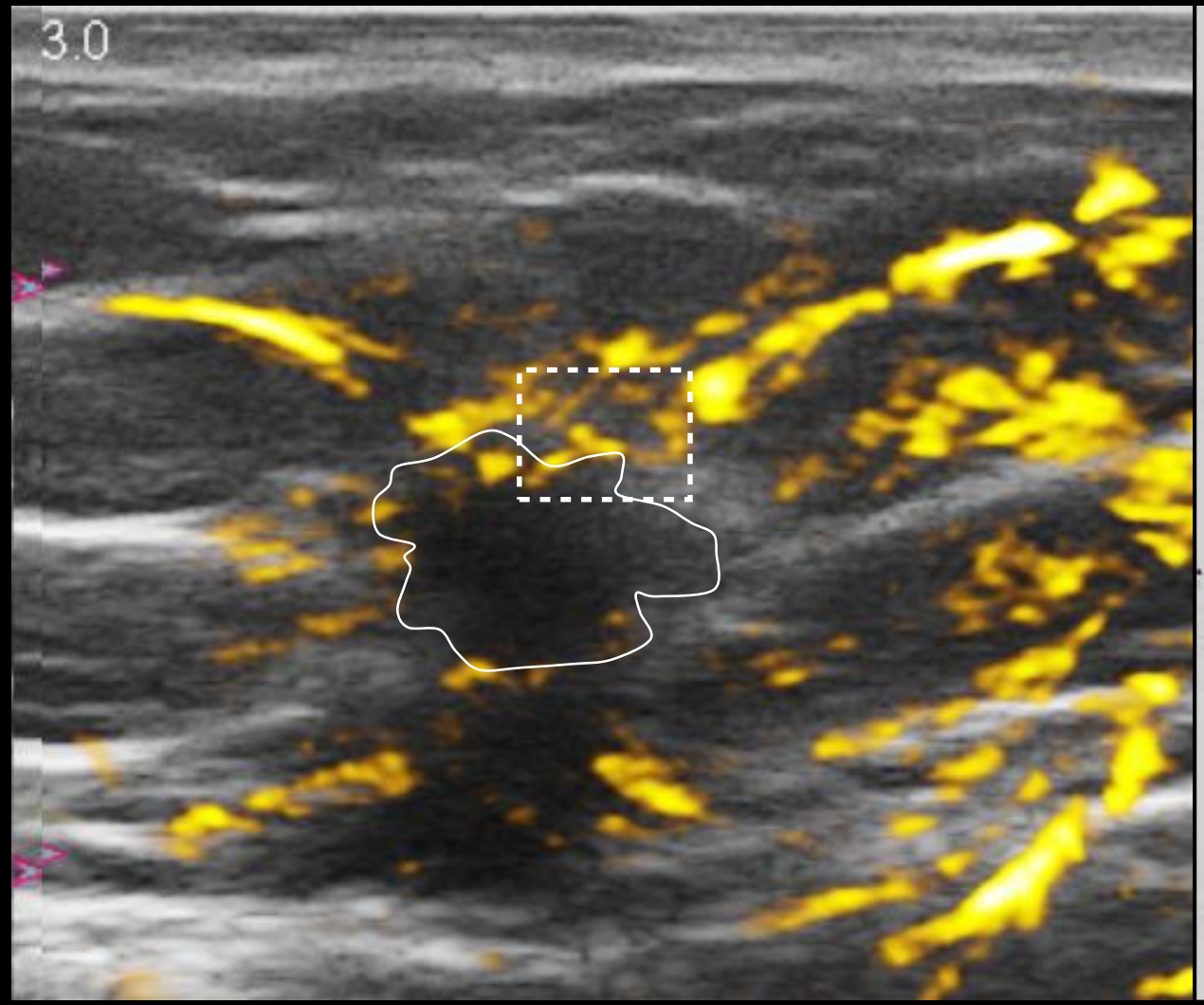
LUMA – Predominantly External Findings

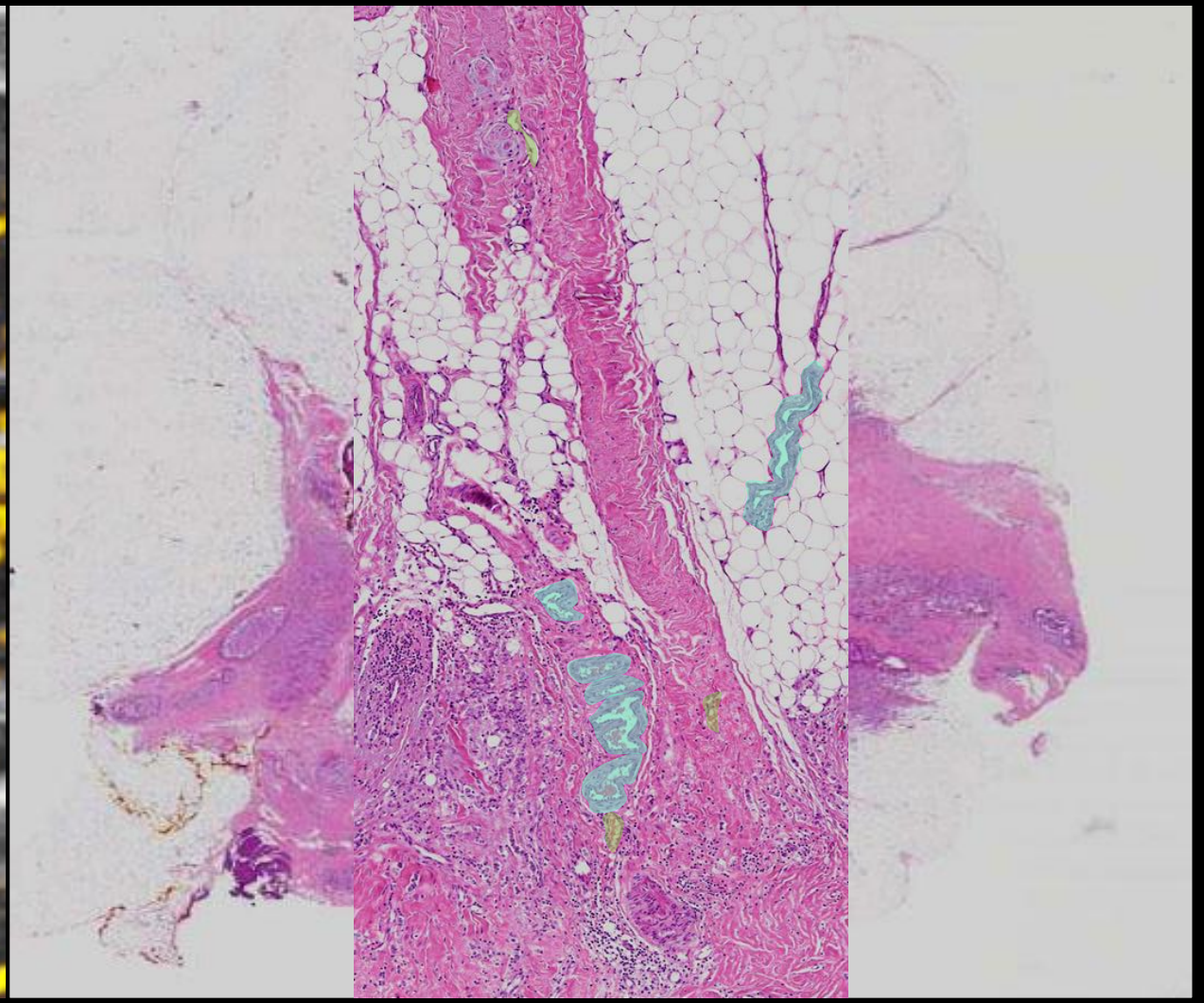




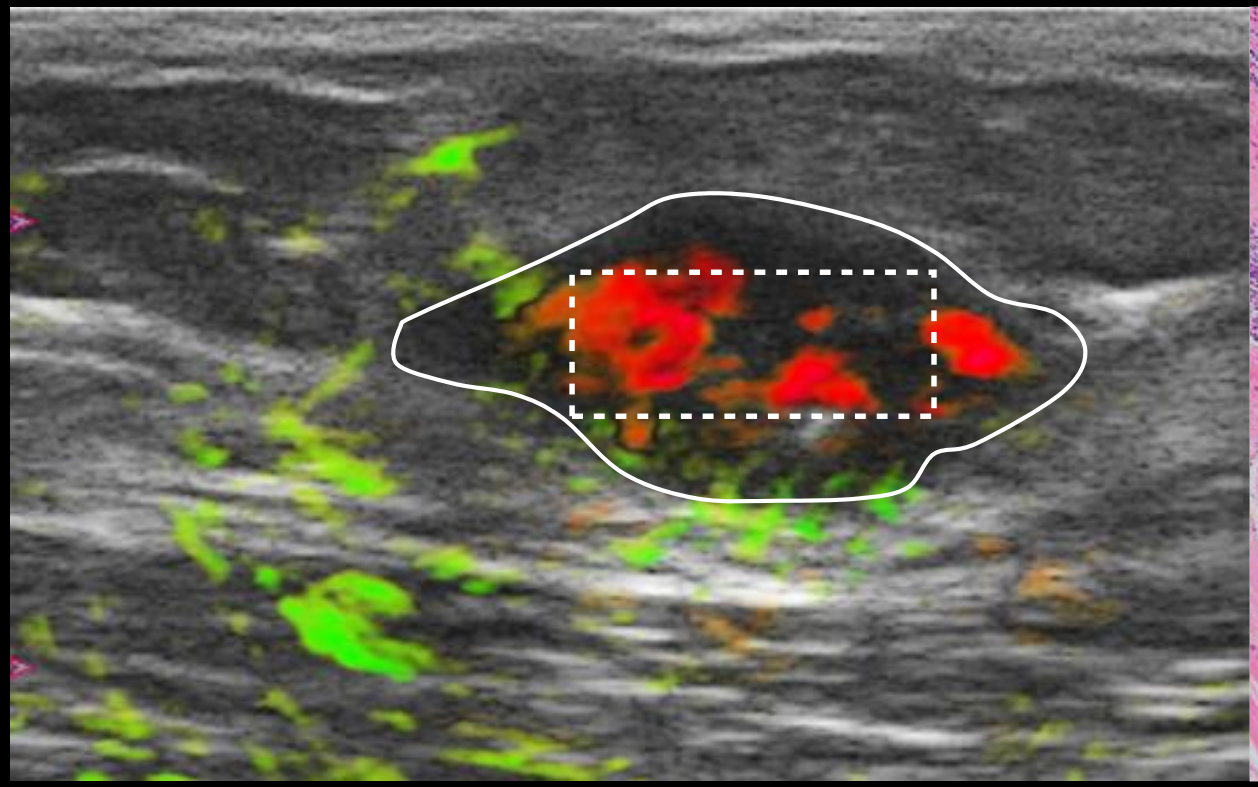


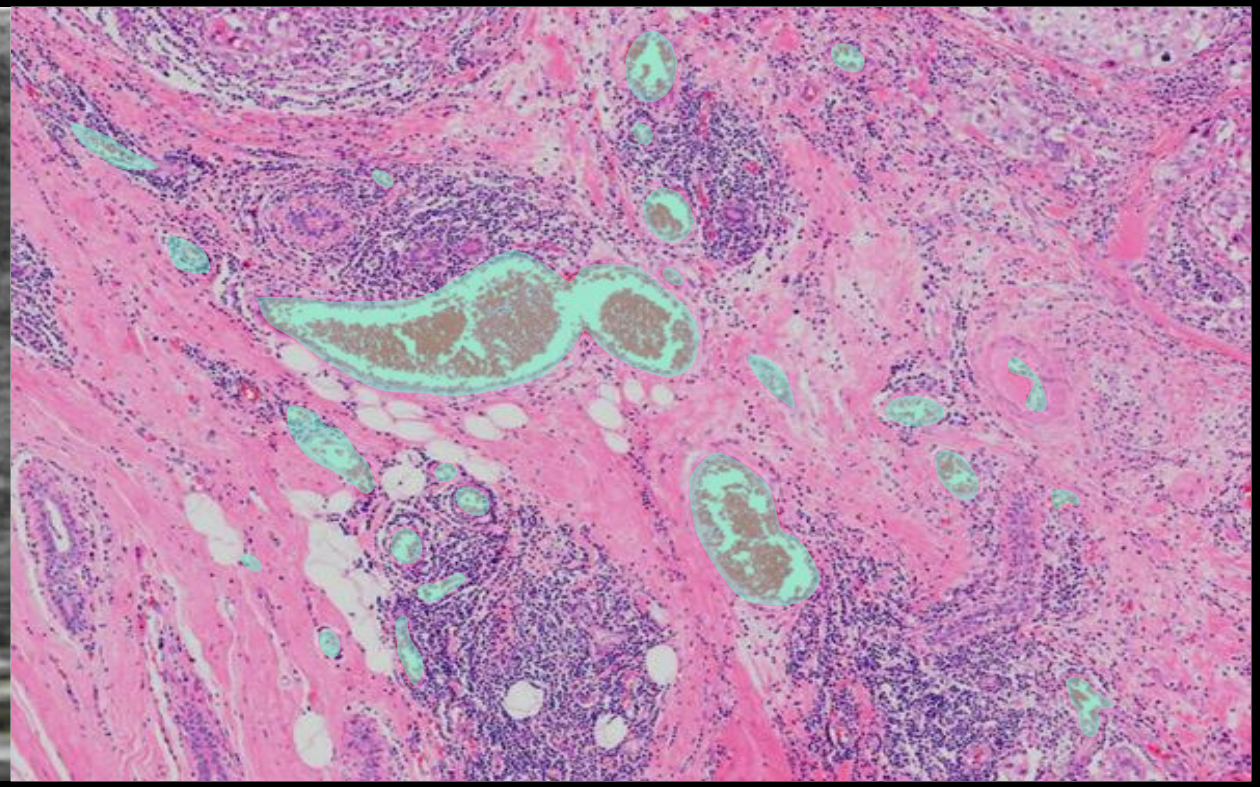
LUMA – Predominantly External Findings



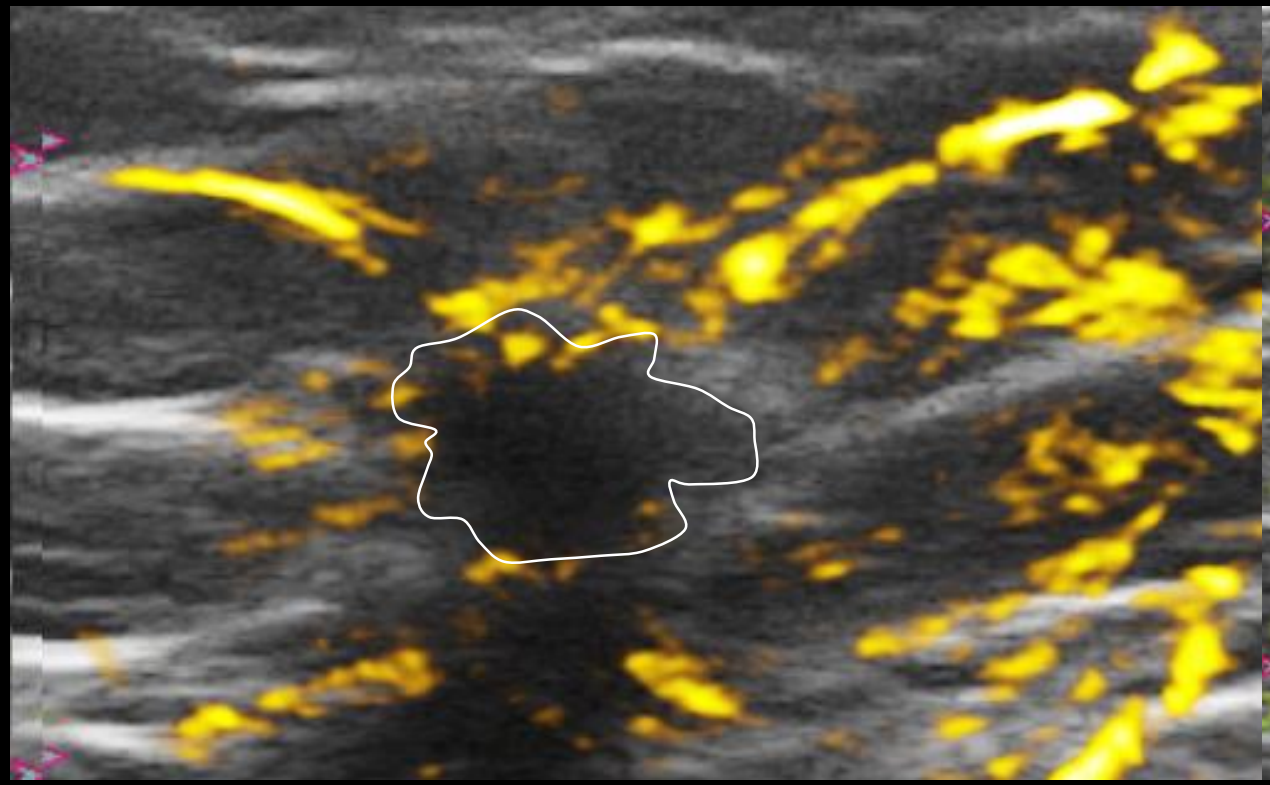


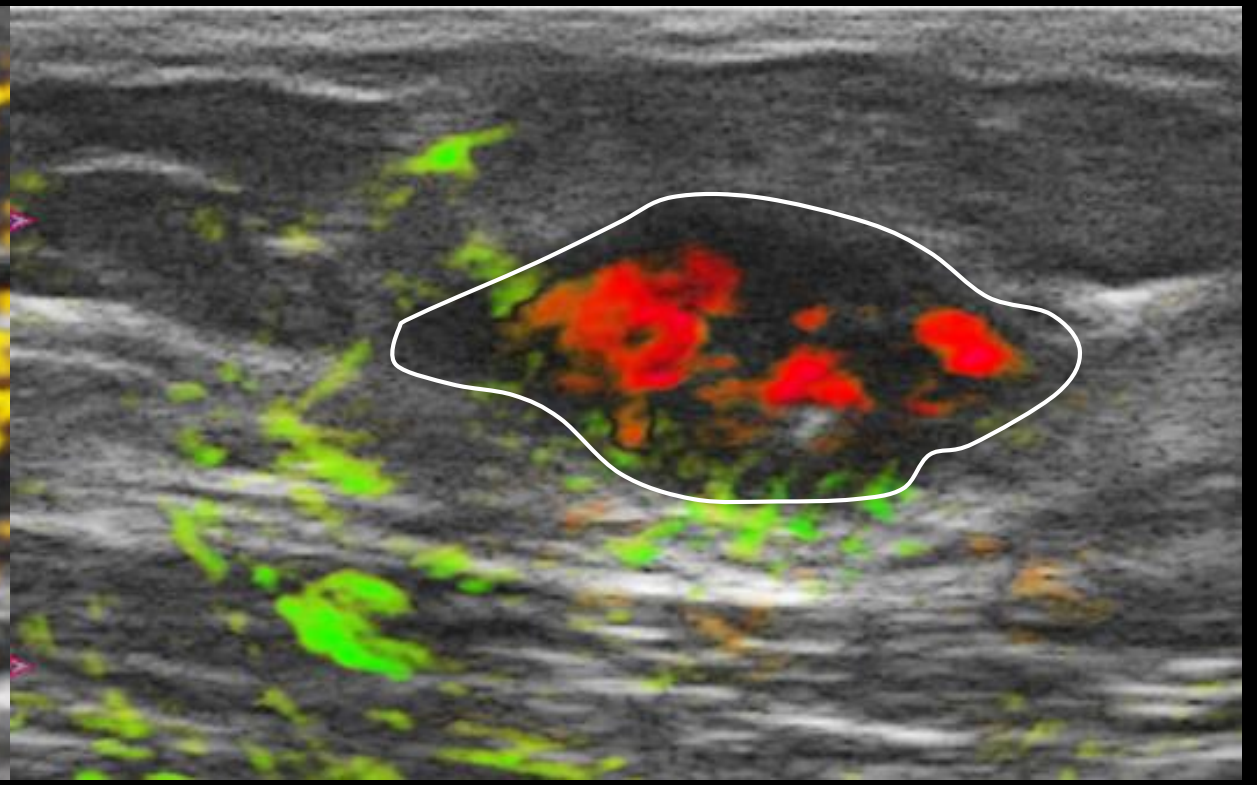
TNBC – Predominantly Internal Findings



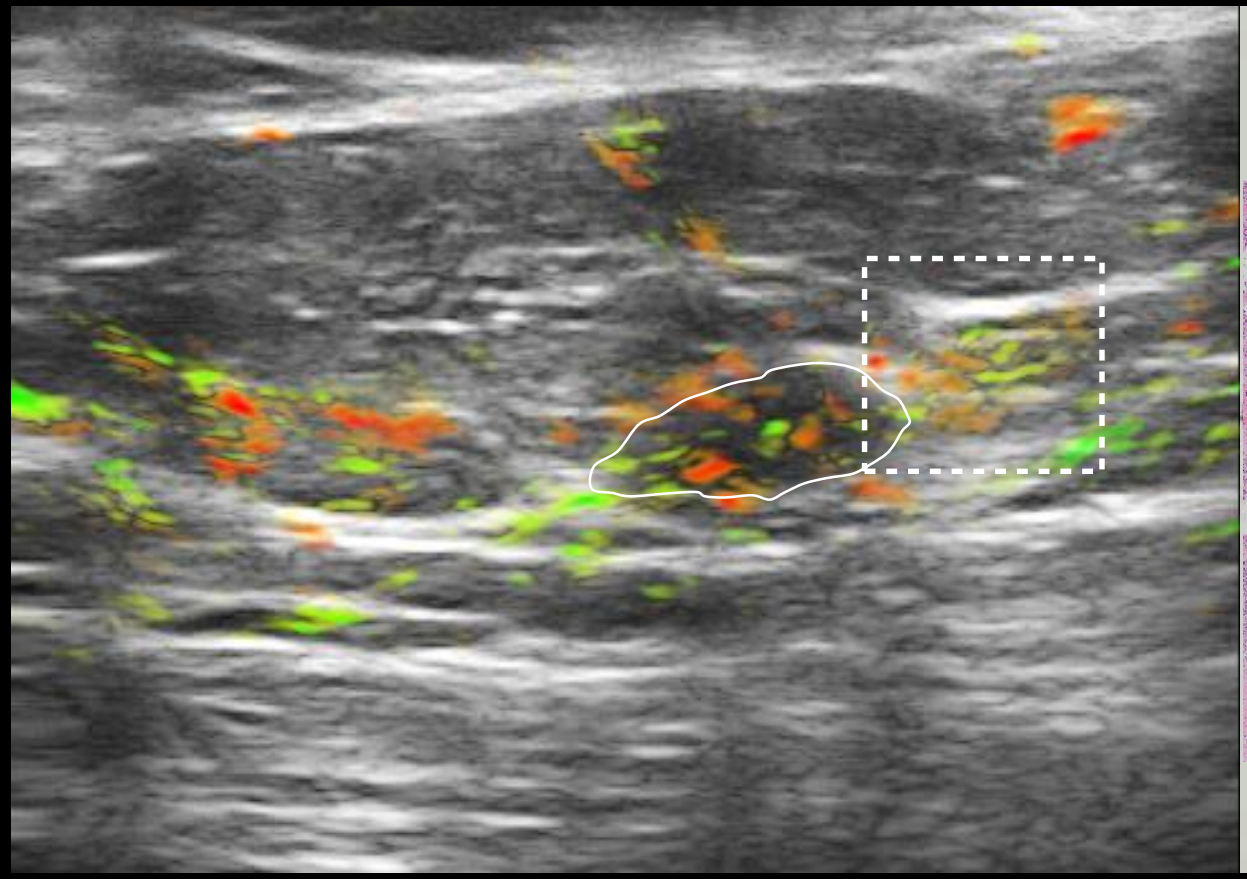


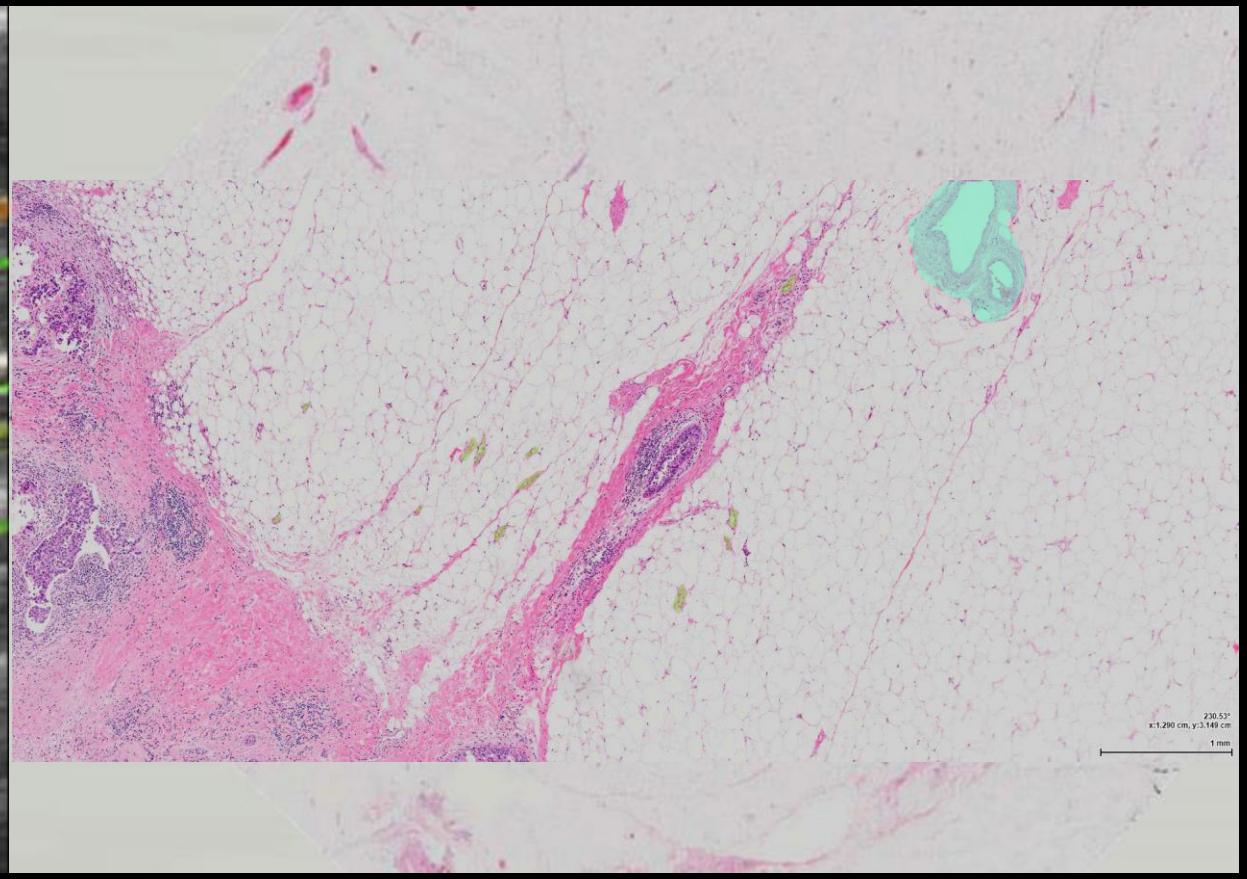
LUMA vs. TNBC



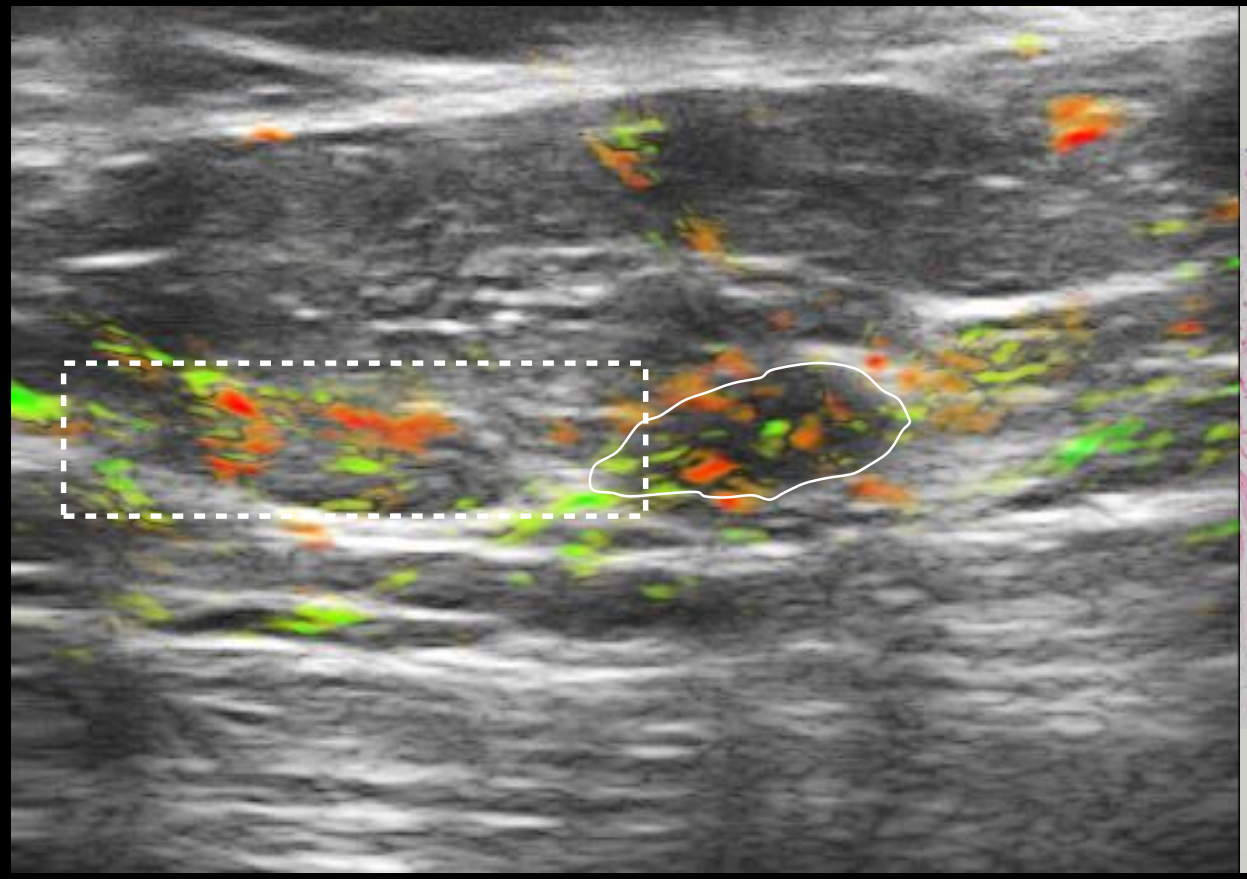


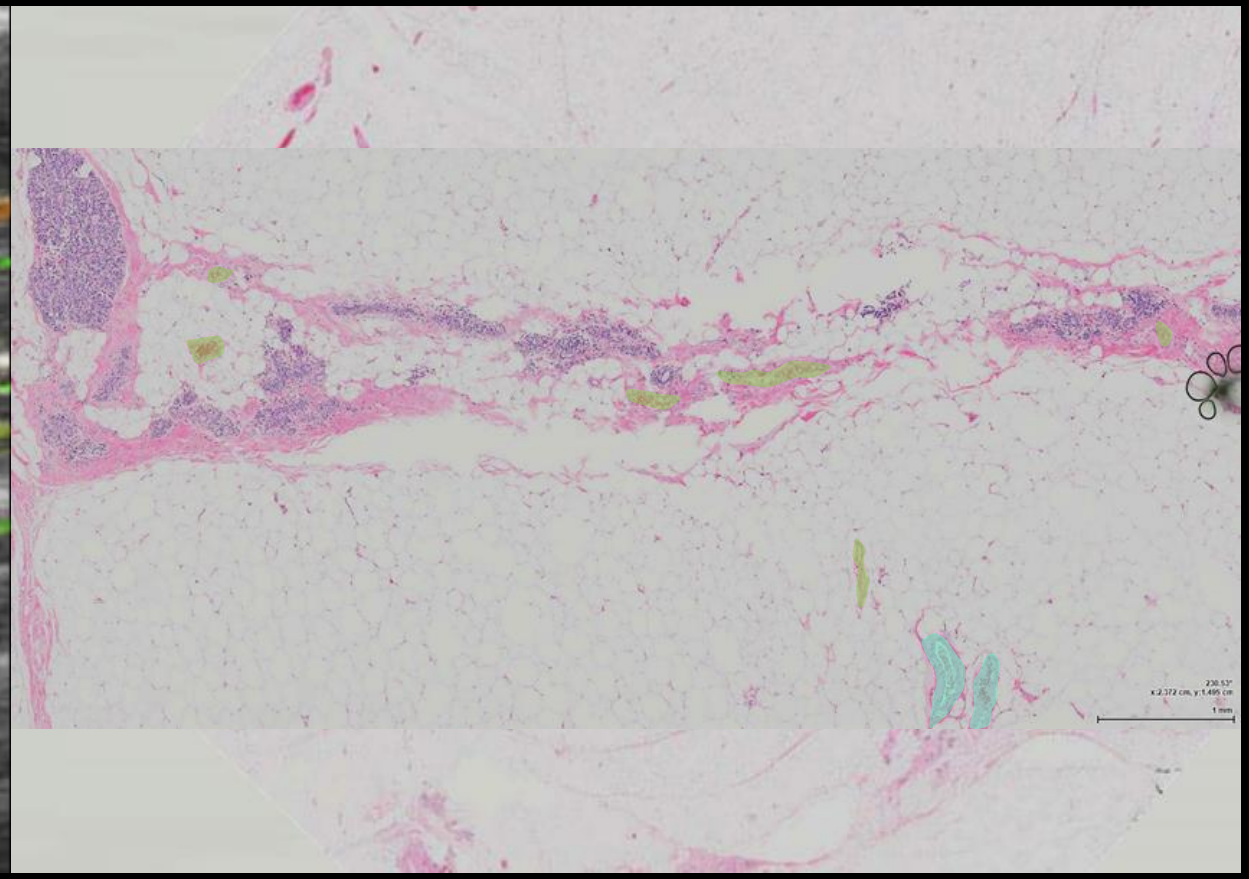
HER2-E – Both Internal and External Findings (External Findings are not so prominent)



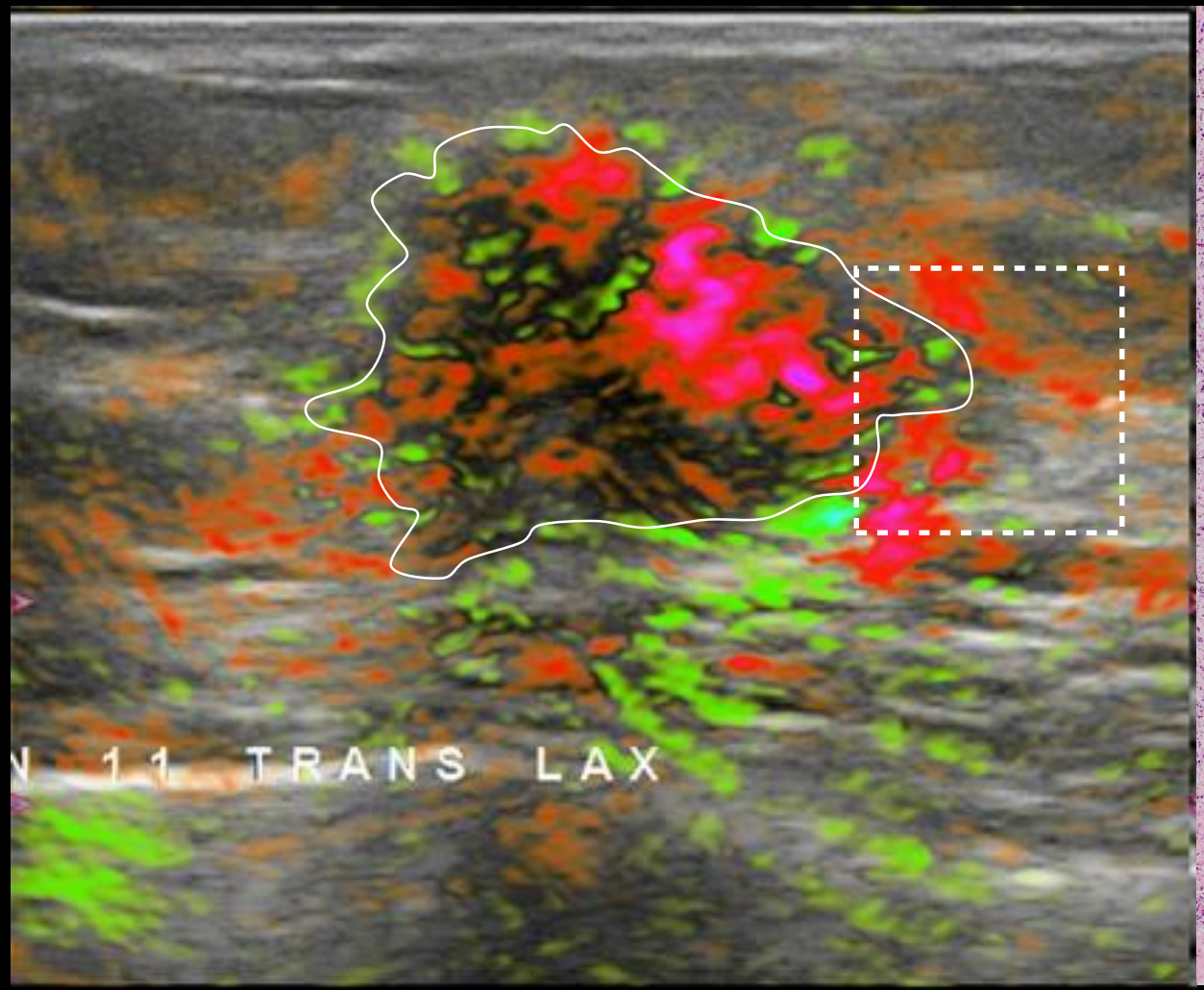


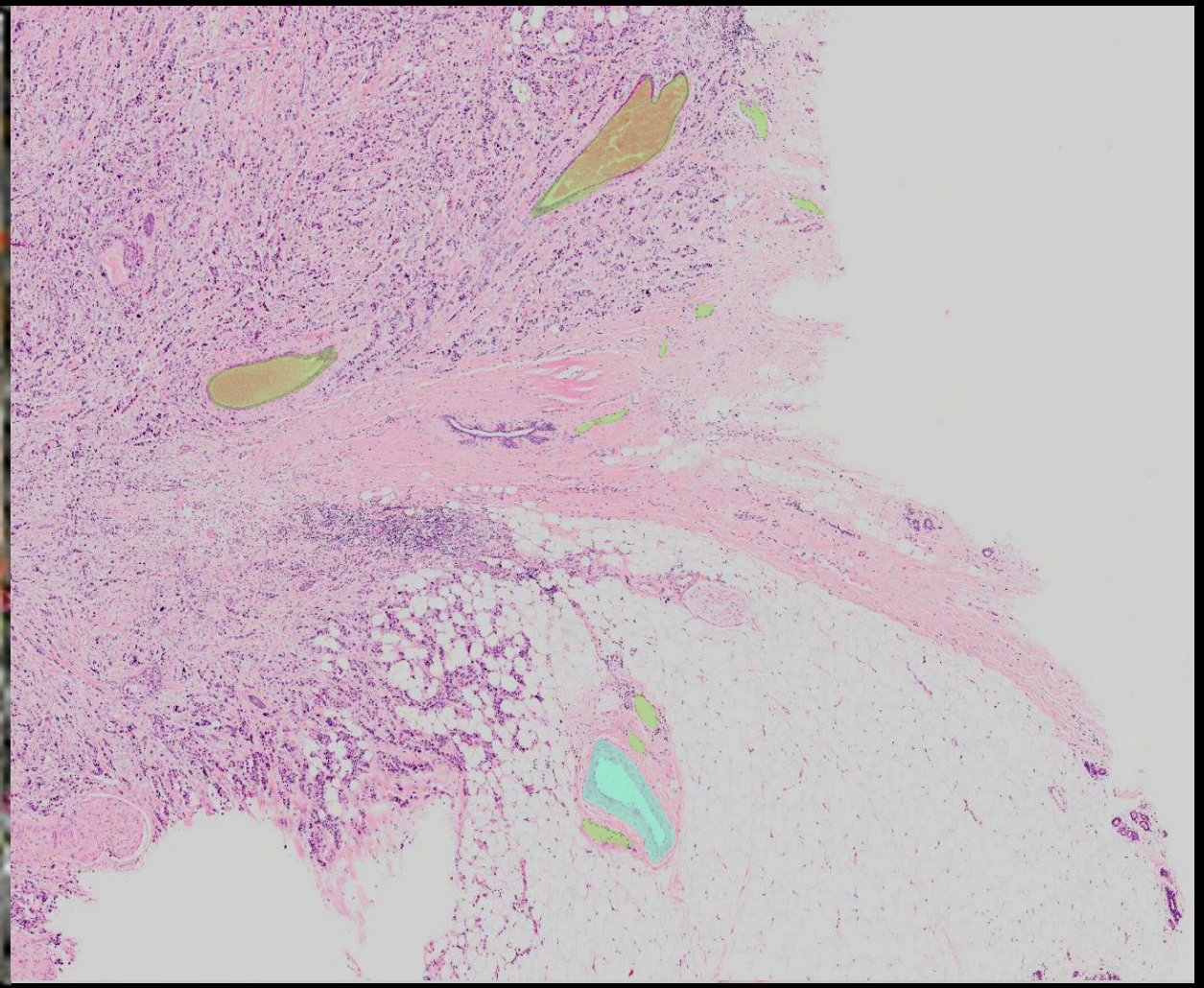
HER2-E – Both Internal and External Findings (External Findings are not so prominent)



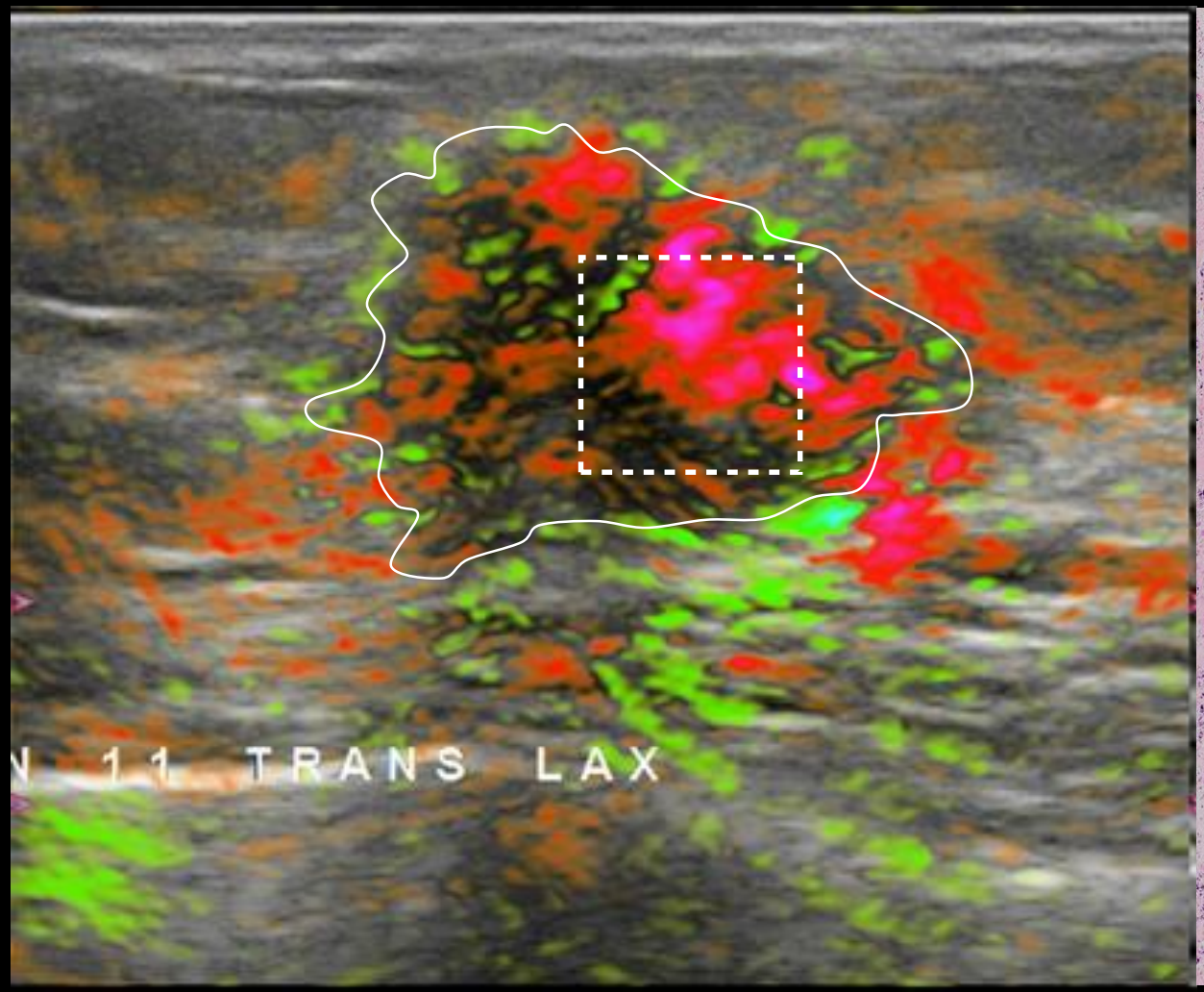


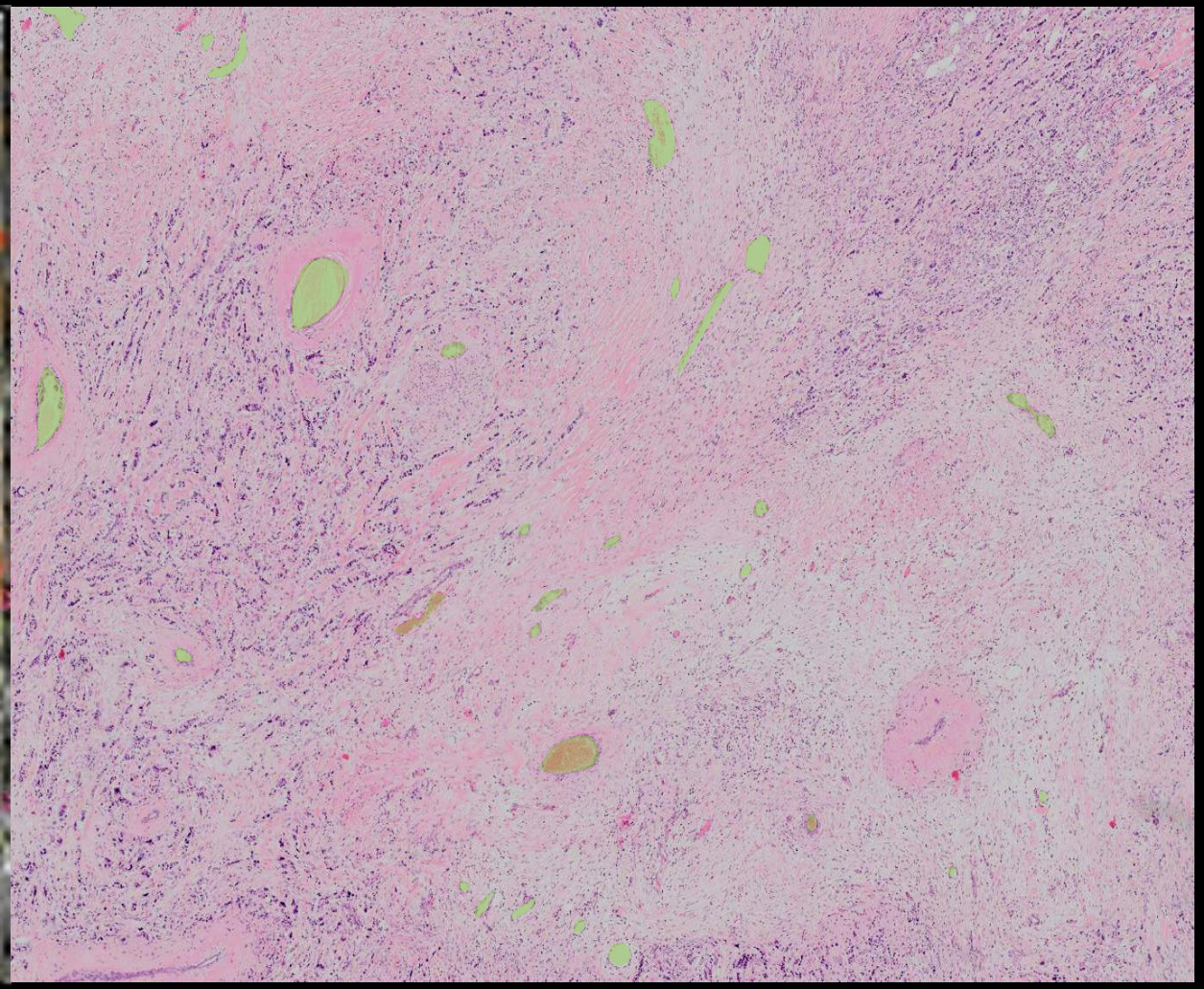
LUMB – Both Internal and External Findings





LUMB – Both Internal and External Findings





Discussion

- Limitations: small number of TNBCs (79) and HER2-E (23). We had 678 malignant masses in the study, but only 532 (78%) masses had molecular subtyping available.
- Breast tumors are usually heterogeneous and biopsy may be insufficient to assess intra-tumoral heterogeneity.
- OA/US might display the dominant feature of the whole tumor.
- If OA/US features don’t match the biopsy findings, it might indicate the need for more extensive histopathologic inspection.

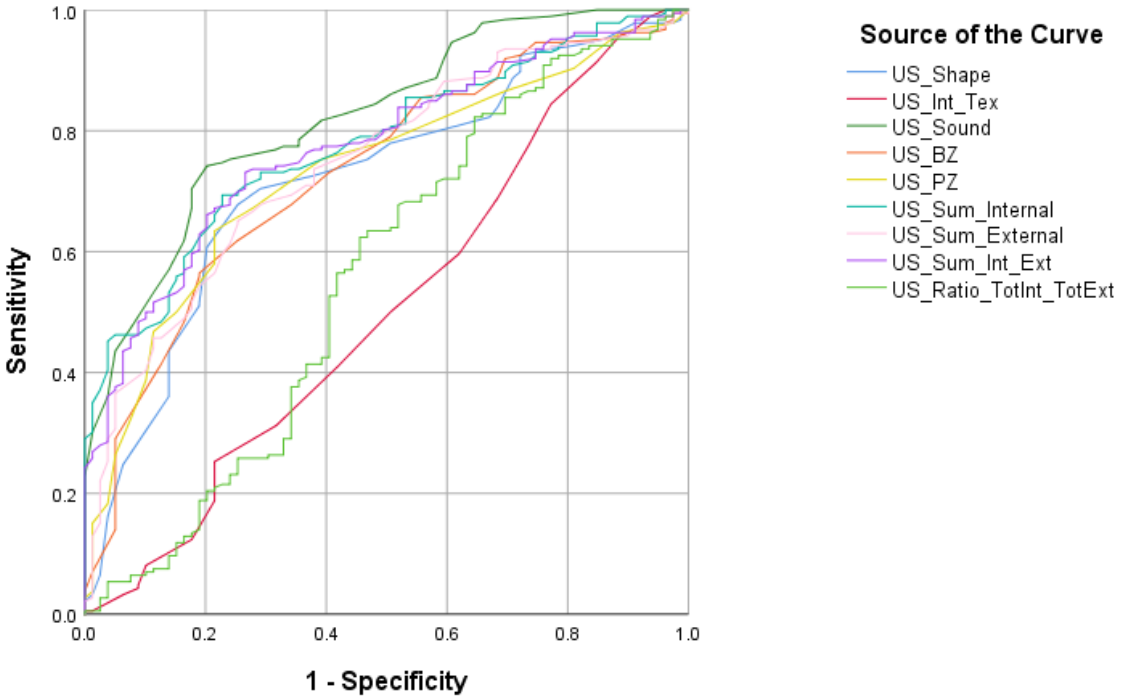
Conclusions

- It is unlikely that OA/US or any other imaging technique will make histologic biomarker analysis unnecessary.
- Nevertheless, OA/US features might help non-invasively distinguish breast cancer molecular subtypes and might facilitate management decisions.

Thank you

LUMA vs TNBC

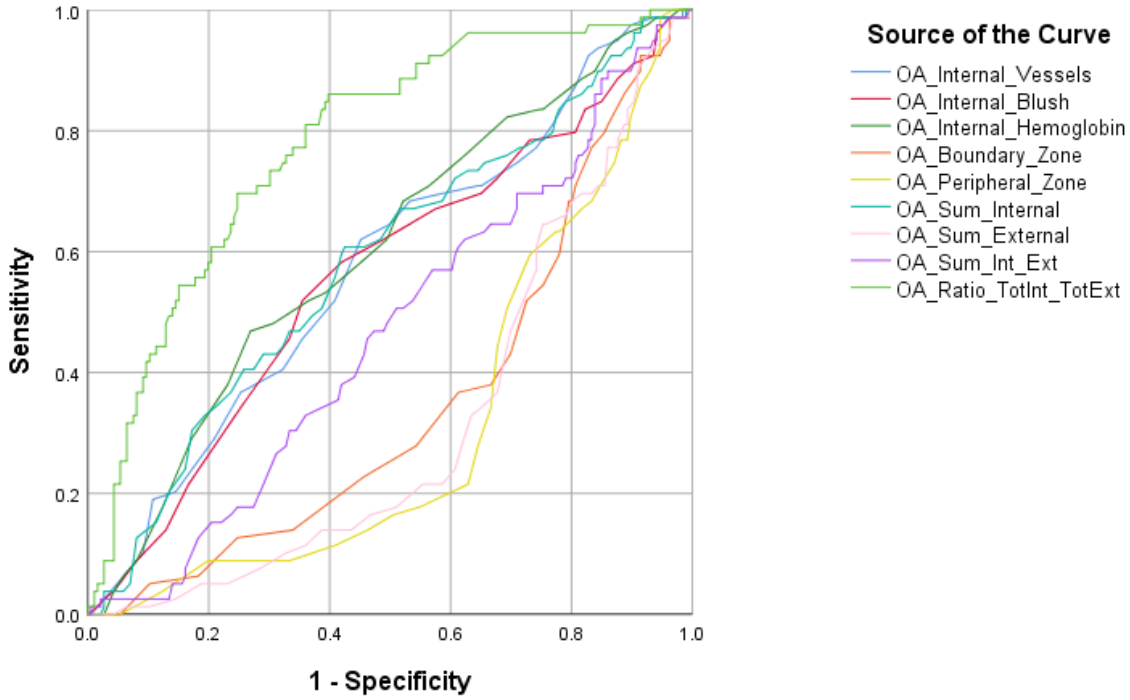
US ROC curves



Area Under the Curve

Test Result Variable(s)	Area
US_Shape	.720
US_Int_Tex	.507
US_Sound	.822
US_BZ	.730
US_PZ	.731
US_Sum_Internal	.778
US_Sum_External	.745
US_Sum_Int_Ext	.775
US_Ratio_TotInt_TotExt	.559

OA ROC curves

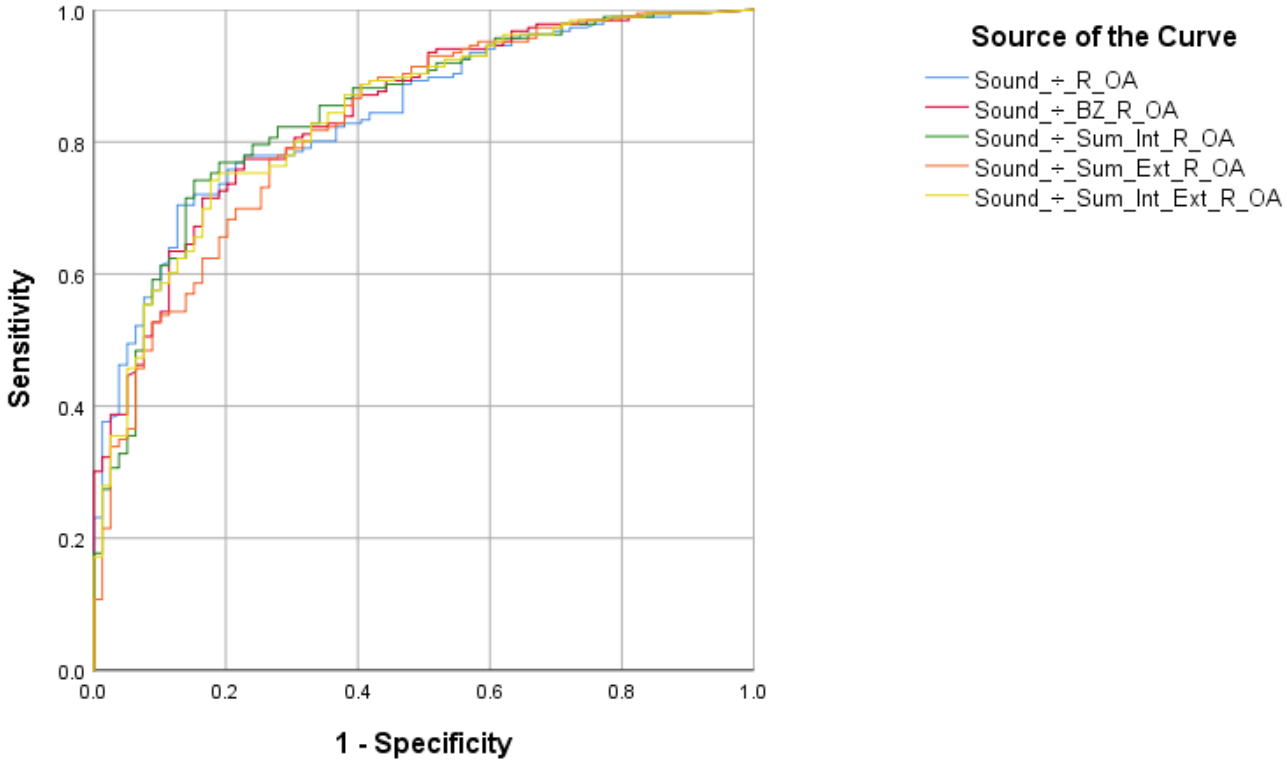


Area Under the Curve

Test Result Variable(s)	Area
OA_Internal_Vessels	.577
OA_Internal_Blush	.562
OA_Internal_Hemoglobin	.602
OA_Boundary_Zone	.353
OA_Peripheral_Zone	.315
OA_Sum_Internal	.585
OA_Sum_External	.319
OA_Sum_Int_Ext	.466
OA_Ratio_TotInt_TotExt	.780

LUMA vs TNBC

US + OA ROC curve

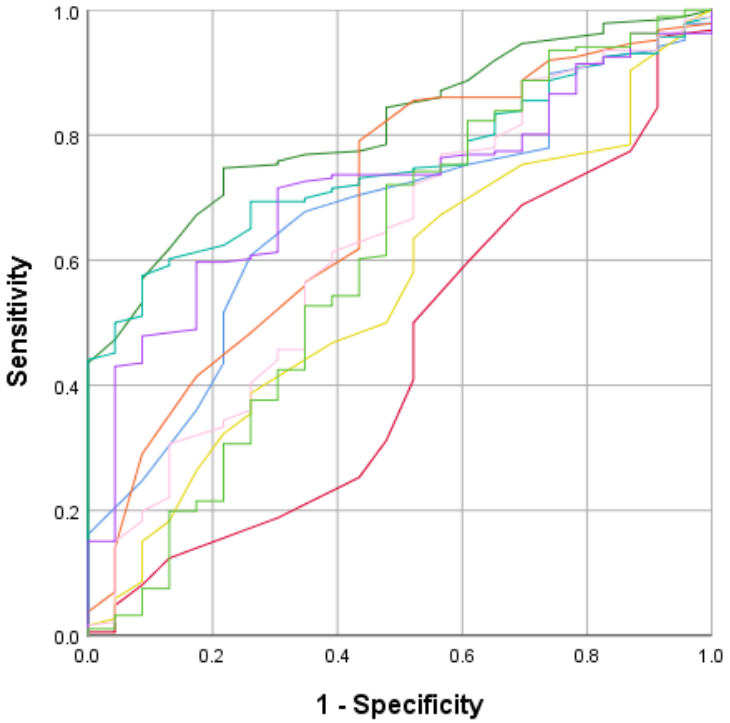


Area Under the Curve

Test Result Variable(s)	Area
Sound_÷_R_OA	.841
Sound_÷_BZ_R_OA	.843
Sound_÷_Sum_Int_R_OA	.845
Sound_÷_Sum_Ext_R_OA	.825
Sound_÷_Sum_Int_Ext_R_OA	.840

LUMA vs HER2-enriched

US ROC curves

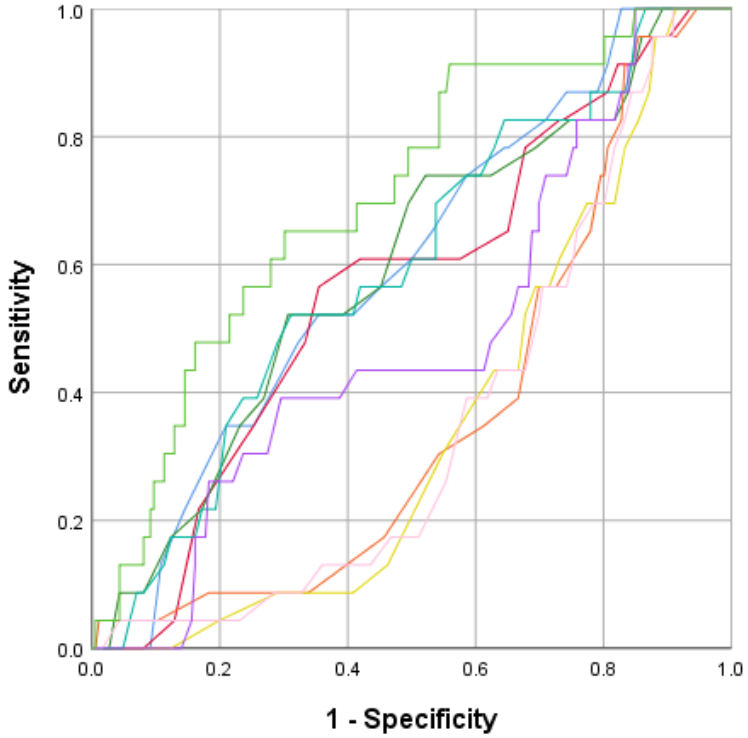


Source of the Curve
- US_Shape
- US_Int_Tex
- US_Sound
- US_BZ
- US_PZ
- US_Sum_Internal
- US_Sum_External
- US_Sum_Int_Ext
- US_Ratio_TotInt_TotExt

Area Under the Curve

Test Result Variable(s)	Area
US_Shape	.672
US_Int_Tex	.441
US_Sound	.813
US_BZ	.686
US_PZ	.549
US_Sum_Internal	.751
US_Sum_External	.625
US_Sum_Int_Ext	.715
US_Ratio_TotInt_TotExt	.602

OA ROC curves

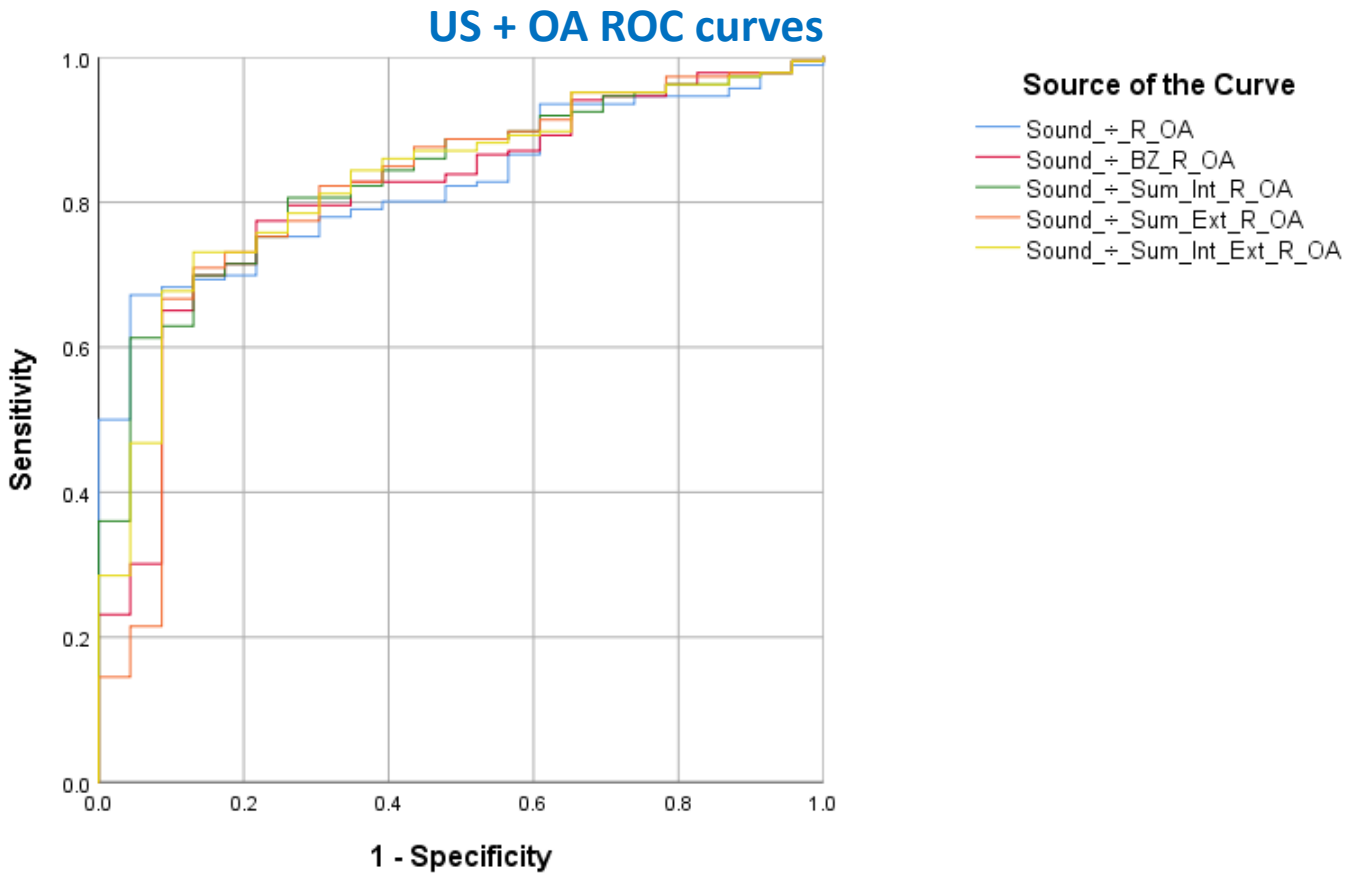


Source of the Curve
- OA_Internal_Vessels
- OA_Internal_Blush
- OA_Internal_Hemoglobin
- OA_Boundary_Zone
- OA_Peripheral_Zone
- OA_Sum_Internal
- OA_Sum_External
- OA_Sum_Int_Ext
- OA_Ratio_TotInt_TotExt

Area Under the Curve

Test Result Variable(s)	Area
OA_Internal_Vessels	.597
OA_Internal_Blush	.567
OA_Internal_Hemoglobin	.597
OA_Boundary_Zone	.368
OA_Peripheral_Zone	.352
OA_Sum_Internal	.596
OA_Sum_External	.358
OA_Sum_Int_Ext	.489
OA_Ratio_TotInt_TotExt	.706

LUMA vs HER2-enriched



Area Under the Curve

Test Result Variable(s)	Area
Sound_÷_R_OA	.827
Sound_÷_BZ_R_OA	.810
Sound_÷_Sum_Int_R_OA	.835
Sound_÷_Sum_Ext_R_OA	.813
Sound_÷_Sum_Int_Ext_R_OA	.830