

Imaging Assessment of TNBC – update on recent advances

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Chinese Redbud

Arnold Arboretum
Boston, MA

I have no disclosures

Outline

- Detection: screening vs diagnostic, multimodality
- Diagnosis: radiologic-pathologic correlation
- Methods on the horizon

Basics

- TNBC represents 10-20% of all breast cancers
- Defined by lack of expression of
 - Estrogen and progesterone receptors
 - Human epidermal growth factor receptor 2
- More often seen in
 - Younger age group
 - African American women
 - Women with genetic mutations, esp BRCA and PALB2
- At diagnosis TNBCs tend to be
 - More advanced stage, higher grade
 - Aggressive with worse prognosis

Detection

- Screening finds
 - earlier and smaller cancers
- Diagnostic
 - Palpable lump
 - Nipple discharge
 - Nipple or skin changes
 - Focal pain
 - Axillary adenopathy

Breast cancer biology varies by method of detection & may contribute to over-diagnosis

Hayes, Hooley et al. Surgery (2016) Vol 160, #2

- From 2004-2014, 2935 cancers detected by one of 5 methods
 - screening mammo
 - screening MRI
 - screening US
 - self-palpated
 - CBE-palpated
- Incidence of low grade cancers
 - 30% in screen detected
 - 11% in palpable group

Breast cancer biology varies by method of detection & may contribute to over-diagnosis

Hayes, Hooley et al. Surgery (2016) Vol 160, # 2

- Image based screening yielded more in situ and T1 cancers ($p < .001$), more luminal cancers
- With more indolent biology
- Symptomatic cancers were more likely high grade, triple negative ($p < .001$)

A comparison of clinical and pathologic characteristics between screen detected and interval cancers

Meshkat et al. The Breast 24 (2015)278-282

- Screen detected cancers
 - 19% DCIS
 - 61% IDC
 - 11% ILC
- Interval cancers
 - 3% DCIS
 - 72% IDC
 - 21% ILC
 - higher grade
 - higher stage (2 vs 1)
 - fewer ER+
 - more Her2 enriched, or basal-like

In other words

- Image-based screening detects lower grade cancers even in dense tissues
- Interval cancers or palpable ones are more aggressive, higher grade, Her2+ or TN
- TN cancers are more likely to present with symptoms rather than be screen detected

Imaging features of BC on DBT according to subtype: association with BC detection

Lee SH, et al. BJR 2017;90(1080)

- Independent blinded review of DBT
- 46 of 288 invasive cancers were TN
- Most common appearances
 - HR + - mass with spiculated margins
 - Her2 + - linear branching Ca⁺⁺
 - TNBC - irregular mass circumscribed margins
- Detectability affected by
 - Tumor size
 - Tissue density
 - Mass vs Ca⁺⁺
 - NOT by subtype

Table 1. Clinical and histological features of 288 invasive breast cancers according to subtype

	Total (n = 288)	Molecular subtype			p-value
		HR+ (n = 194)	HER2+ (n = 48)	TNBC (n = 46)	
Age (years)					0.190
Mean (SD)	50.8 (10.6)	50.0 (10.1)	52.5 (11.1)	52.4 (11.9)	
Median (range)	49 (22–78)	48 (22–77)	52 (30–73)	52 (30–78)	
Clinical manifestation					0.027
Asymptomatic	85 (29.5)	67 (34.5)	9 (18.8)	9 (19.6)	
Palpable lump	203 (70.5)	127 (65.5)	39 (81.2)	37 (80.4)	
FHx of breast cancer					0.793
Absent	272 (94.4)	184 (94.8)	45 (93.8)	43 (93.5)	
Present	16 (5.6)	10 (5.2)	3 (6.3)	3 (6.5)	
Histological type					0.004
Ductal, NOS	248 (86.1)	159 (82.0)	48 (100)	41 (89.1)	
Dctal, special	18 (6.3)	14 (7.2)	0 (0)	4 (8.7)	
Lobular	22 (7.6)	21 (10.8)	0 (0)	1 (2.2)	
Focality					0.006
Unifocal	205 (71.2)	135 (69.6)	29 (60.4)	41 (89.1)	
Multifocal	83 (28.8)	59 (30.4)	19 (39.6)	5 (10.9)	
Tumour size (cm)					0.639
Mean (SD)	2.3 (1.3)	2.2 (1.3)	2.2 (1.1)	2.4 (1.2)	
Median (range)	2.0 (0.1–9.5)	2.0 (0.1–9.5)	2.1 (0.2–5.3)	2.2 (0.4–7.7)	
Histological grade					<0.001
1 or 2	138 (47.9)	127 (65.5)	5 (10.4)	6 (13.0)	
3	150 (52.1)	67 (34.5)	43 (89.6)	40 (87.0)	
Associated DCIS					0.087
Absent	57 (19.8)	42 (21.6)	4 (8.3)	11 (23.9)	
Present	231 (80.2)	152 (78.4)	44 (91.7)	35 (76.1)	
Lymphovascular invasion					0.002
Absent	207 (71.9)	144 (74.2)	25 (52.1)	38 (82.6)	
Present	81 (28.1)	50 (25.8)	23 (47.9)	8 (17.4)	
Axillary lymph node metastasis					0.159
Absent	203 (70.5)	136 (70.1)	30 (62.5)	37 (80.4)	
Present	85 (29.5)	58 (29.9)	18 (37.5)	9 (19.6)	
Ki-67 index					<0.001
Low (<14%)	236 (81.9)	183 (94.3)	31 (64.6)	22 (47.8)	
High (≥14%)	52 (18.1)	11 (5.7)	17 (35.4)	24 (52.2)	

Summary Table 1: Comparison of HR+, Her2+ & TNBC

• Age (yrs)	No difference - 50, 52, 52
• Palpability (%)	66, 81, 80
• FH	No difference – absent >90%
• Ductal (%)	82, 100, 89
• Size	No difference
• Unifocal	TN more likely
• Grade	Higher for Her2 and TNBC
• LVI	Less likely in TNBC
• LN mets (%)	30, 38, 20 – less likely in TNBC
• Ki67 (%)	6, 35, 52

Table 2. Imaging features of 288 invasive BC on DBT according to subtype

	HR+ (n = 194)	HER2+ (n = 48)	TNBC (n = 46)	p-value
Breast density				0.923
a	8 (4.1)	2 (4.2)	3 (6.5)	
b	29 (14.9)	9 (18.8)	9 (19.6)	
c	114 (58.8)	27 (56.2)	26 (56.5)	
d	43 (22.2)	10 (20.8)	8 (17.4)	
a-b (non-dense)	37 (19.0)	11 (23.0)	12 (26.1)	0.532
c-d (dense)	157 (81.0)	37 (77.0)	34 (73.9)	
Lesion type on DBT				<0.001
Negative (not visible)	9 (4.6)	0 (0)	2 (4.3)	
Focal asymmetry	6 (3.1)	1 (2.1)	1 (2.2)	
Calcifications only	11 (5.7)	12 (25.0)	4 (8.7)	
Mass only	110 (56.7)	9 (18.8)	21 (45.7)	
Mass with calcifications	58 (29.9)	26 (54.2)	18 (39.1)	
Presence of mass				0.068
Yes	168 (86.6)	35 (72.9)	39 (84.8)	
No	26 (13.4)	13 (27.1)	7 (15.2)	
Mass shape ^a				<0.001
Oval	10 (6.0)	4 (11.4)	10 (25.6)	
Round	11 (6.5)	5 (14.3)	8 (20.5)	
Irregular	147 (87.5)	26 (74.3)	21 (53.8)	
Mass margin ^a				<0.001
Circumscribed	18 (10.7)	4 (11.4)	13 (33.3)	
Obscured	4 (2.4)	1 (2.9)	4 (10.3)	
Microlobulated	18 (10.7)	8 (22.9)	7 (17.9)	
Indistinct	32 (19.0)	10 (28.6)	6 (15.4)	
Spiculated	96 (57.1)	12 (34.3)	9 (23.1)	
Presence of calcifications				<0.001
Yes	68 (35.1)	38 (79.2)	22 (47.8)	
No	126 (64.9)	10 (20.8)	24 (52.2)	
Calcification morphology ^b				<0.001
Amorphous	35 (51.5)	8 (21.1)	14 (63.6)	
Coarse heterogeneous	9 (13.2)	2 (5.3)	0 (0)	
Fine pleomorphic	21 (30.9)	17 (44.7)	7 (31.8)	
Fine linear or linear branching	3 (4.4)	11 (28.9)	1 (4.5)	

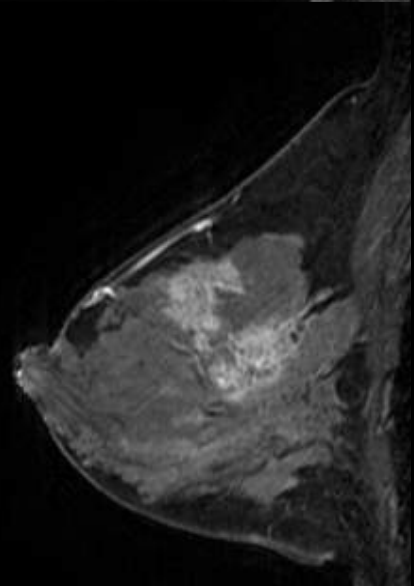
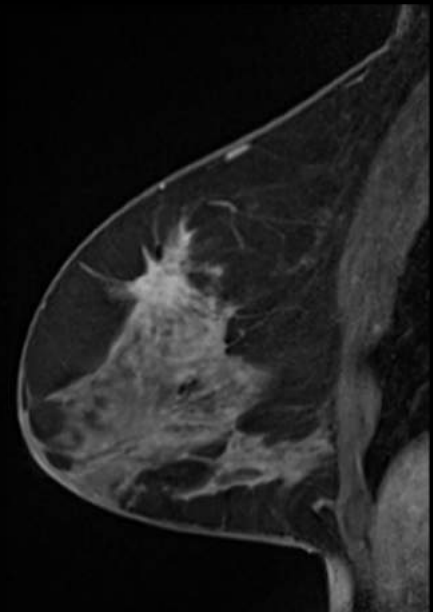
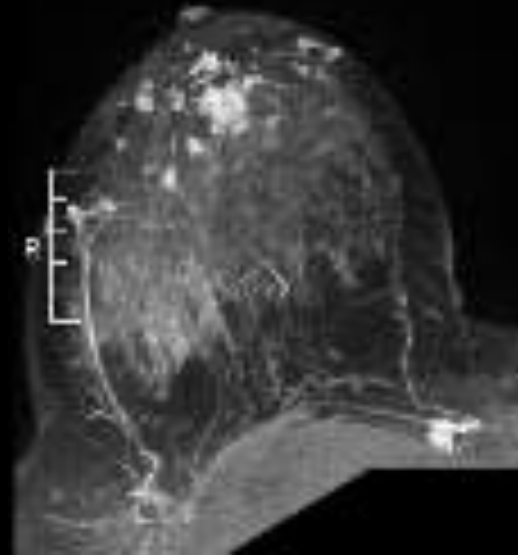
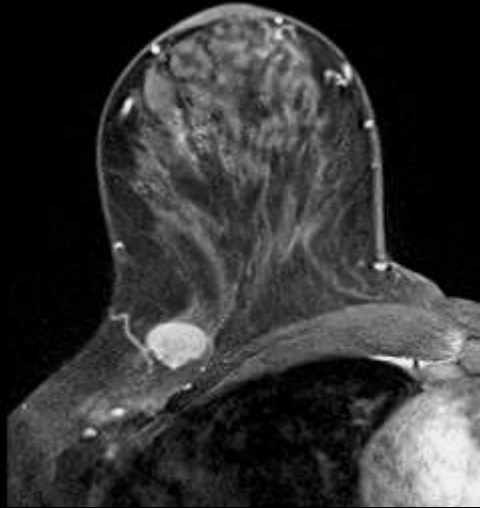
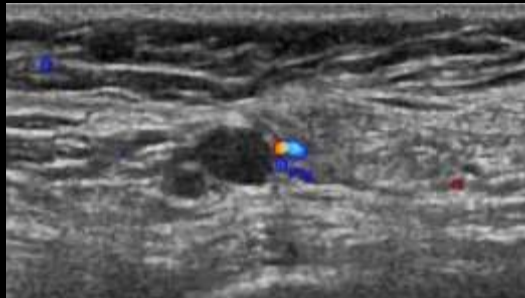
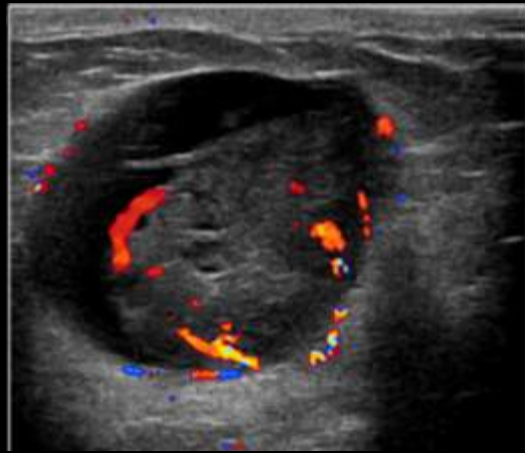
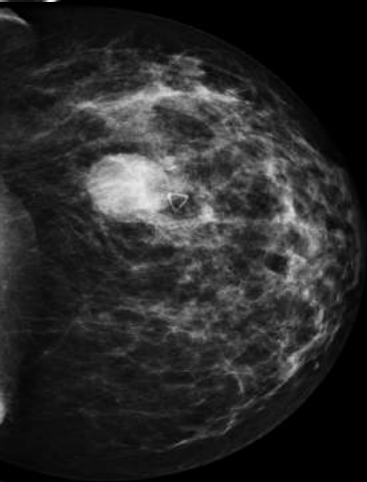
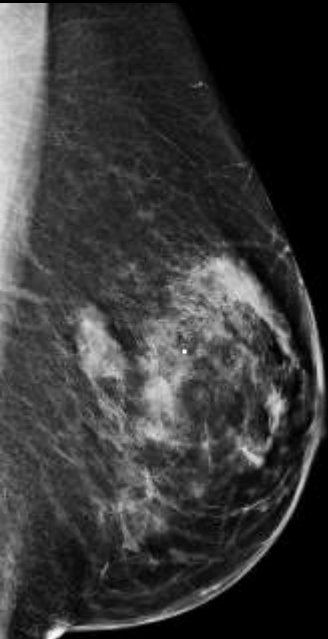
Summary Table 1: Comparison of HR+, Her2+ & TNBC

- Density – 74 – 81 % cancers in dense tissues
- Lesion type – most were masses +/- Ca++
- Mass shape
 - % irregular - 88, 74, 54
 - % oval - 6, 11, 26
- Margins
 - Circumscribed - 11, 11, 33
 - Non-circ - 89, 89, 67
 - Spiculated - 57, 34, 23
- Calcifications - 35, 80, 48

Summary

- Author's key conclusions
 - DBT showed characteristic imaging features based on molecular subtype
 - detectability on DBT not affected by molecular subtype
- My conclusions
 - TNBC more likely to present with symptoms
 - More often in dense tissues
 - May be regular shapes – more often than luminal BC
 - May be circumscribed - more often than luminal BC
 - BUT majority will still be irregular shape and margins

Imaging phenotypes?

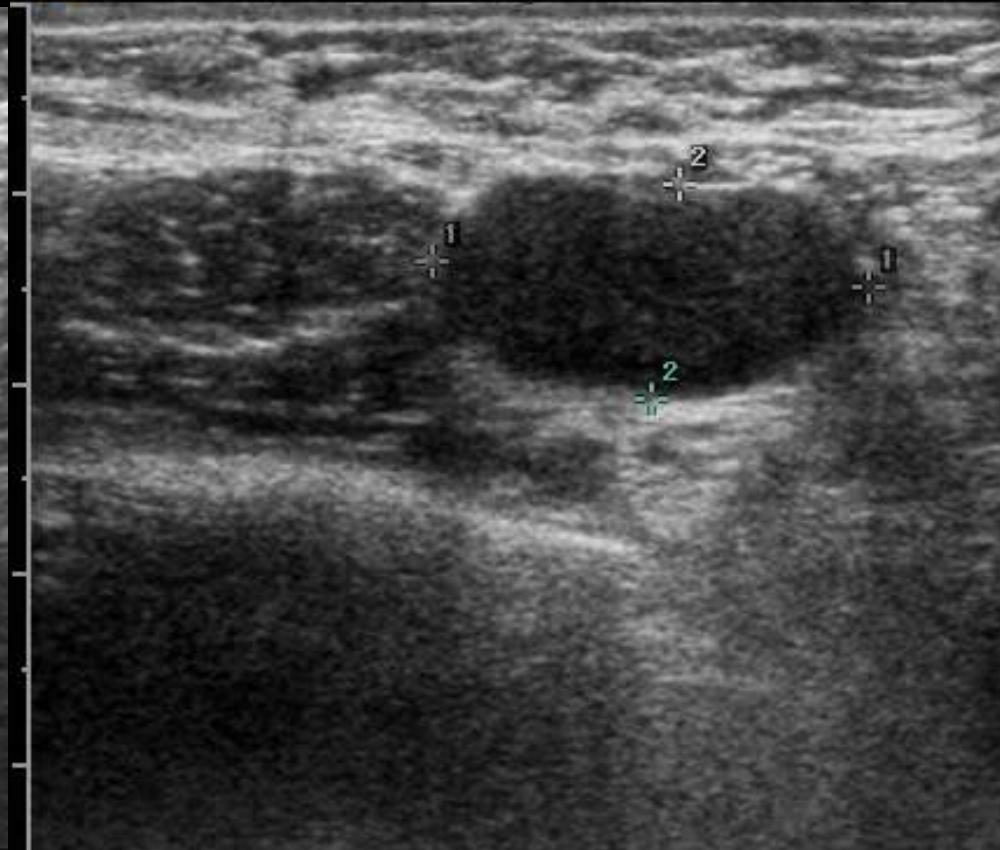
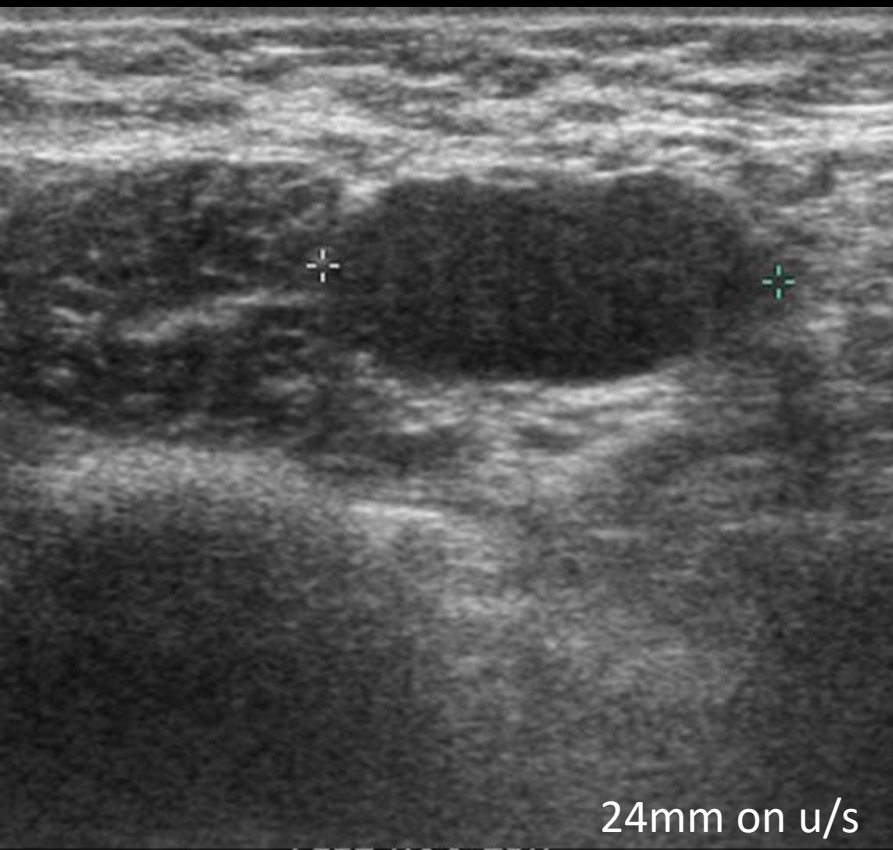


Molecular subtypes and imaging phenotypes of breast cancer

Cho N. Ultrasonography. 2016 Oct; 35(4): 281–288.

- Linking US imaging with molecular subtype
 - non-calcified, circumscribed masses with posterior acoustic enhancement are common in the basal-like subtype
 - spiculated masses with non-circumscribed margin and shadowing in the luminal subtype
 - pleomorphic calcifications in the HER2-enriched subtype
- Generally
 - Aggressive tumors have outwardly convex margins
 - Slow growing tumors incite a response seen as spiculated margins

42 yo with palpable lump



Heterogeneity of TNBC: mammographic, US, and MRI features according to androgen receptor expression

Bae MS, et al. Eur Radiol. 2015 Feb;25(2):419-27

- 125 TN cancers of 1086 invasive breast cancers
- 2 radiologists reviewed imaging
- Features of AR+ tumors
 - Calcifications on mammo +/- mass
 - NME on MRI
 - Mass with irregular shape and/or spiculated margins on US and MRI
 - More likely to have DCIS (91% vs 60%)
 - More likely to have lower Ki-67 exp (30% vs 52%)

Imaging Features of TNBC According to Androgen Receptor Status

Candelaria RP, et al. Eur J Radiol. 2019(114)167-174

- 144 pts with stage 1-3 TNBC undergoing NAT
 - 45 (31%) AR+ and 99 AR- (69%)
- AR+ defined as $\geq 10\%$ tumor cells with AR staining
- Univariate analysis \rightarrow sig association of AR+ cases with
 - Heterogeneously dense tissue on mammo
 - Mass with calcifications
 - Irregular mass shape on mammo and US

Imaging Features of TNBC According to Androgen Receptor Status

- Trends noted n MRI

Feature	AR +	AR -
Mass	100	87
Oval or round shape	56	76
Non-circumscribed	81	51

Clinical Imaging of the Heterogeneous Group of TNBC

Müller M Anticancer Res. 2020;40(4):2125-2131

- 135 patients with TNBC
- Imaging features by subtype
 - Basal-like – BL
 - Mesenchymal-like - ML
 - Luminal Androgen Receptor – LAR
 - Immunomodulatory – IM
- LAR-TNBC were more often spiculated (24% vs 0-4%)
- BL-TNBC more often a mass no Ca++ (71% vs 48-58%)
- ML-TNBC more often circumscribed on US
- Features likely reflect different growth patterns

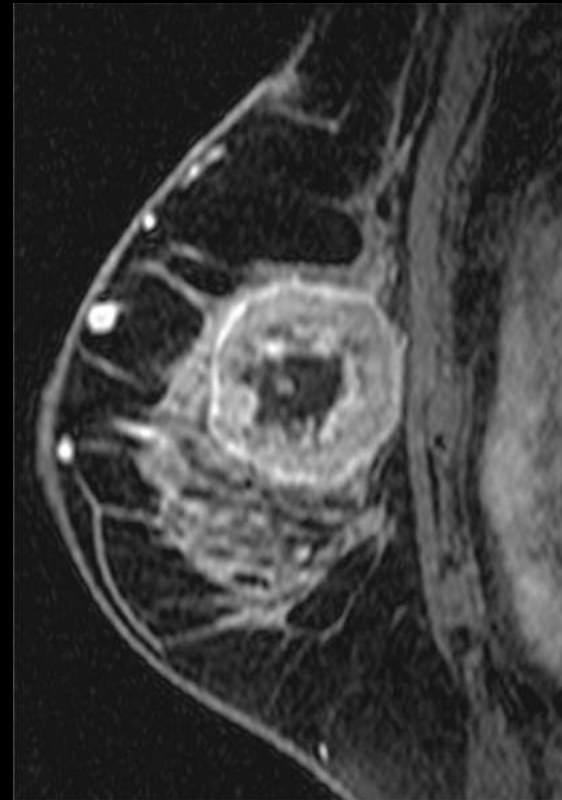
MRI features of TNBC

- Morphological analysis → similar to mammo and US
- Internal enhancement patterns differ
- 2013 study MSKCC
 - 140 pts with TNBC c/w 181 Luminal A cancers
 - MRs reviewed by 2 radiologists
- TNBC
 - Larger size, higher grade, and unifocal
 - Rim enhancing mass, lobular shape, smooth margins
 - Areas of high T2 signal
 - Central necrosis

Triple-negative breast cancer: correlation between MR imaging and pathologic findings

Uematsu T, et al. Radiology. 2009 Mar;250(3):638-47

- Features significantly associated with TNBC
 - high histologic grade ($P < .001$)
 - unifocal lesion ($P = .012$)
 - mass lesion type ($P < .001$)
 - smooth margins ($P = .001$)
 - rim enhancement ($P < .001$)
 - high T2 signal ($P = .002$)
 - persistent kinetics ($P = .005$)



Value of DCE MRI in diagnosis & management of TNBC

Azzam et al. Egypt J Radiol(51):article 26, 2020

- 100 patients with 172 TNBC (80% IDC, 16% ILC)
 - Mean age 45
- 104/172 (61%) masses, 52 (30%) NME, 16 (9%) foci
- Mass shape: 62% irregular, 38% round or oval
- All masses enhanced – 46% rim enhancing
- High T2 signal in 63% of all cases
- Kinetics: 45% washout, 39% plateau, 16% persistent

Can MRI Biomarkers Predict TNBC?

Moff G, et al. Diagnostics (Basel).2020;10(12):1090

- 26 TNBC c/w 24 non-TNBC cancers
- 2 radiologist evaluated images
- 92% of all cases were enhancing masses

Feature	TNBC (%)	Non-TNBC (%)
Round or oval shape	58	14
Circumscribed margins	58	9
Rim enhancement*	75	9
Intralesional necrosis	42	8

*Rim enhancement is independently associated with TNBC (OR = 33.08)

- Mean ADC on DWI sig higher in TNBC

Background Parenchymal Enhancement As An Imaging Bridge To Molecular Cancer Sub-Type

Dilorenzo G, et al. Eur J Radiol 113, Feb 2019

- Total consecutive BC cases with MRI = 82
- 18/82 (22%) were TN
- 16/82 cases had marked BPE of which 10 were TNBC (sig)
- BPE in 18 TNBC cases (not sig)
 - 10 marked
 - 6 moderate
 - 2 mild
 - 0 minimal
- Luminal and Her2 types were mostly Mild to Moderate
- Does less BPE indicate more favorable prognosis in TNBC??

Radiomics features to identify distinct subtypes of triple-negative breast cancers

Itakura H, et al. JCO 37(15), 2019

- 117 TNBC lesions in 90 patients - mean age 49
- Radiomics features extracted from MRI via active segmentation
- 900 radiomics features including
 - 3 distinct image-based clusters with distinct biomarkers, similar mean age and stage distribution
- Among those receiving NAT, pCR in
 - 50% Cluster 1
 - 83% Cluster 2
 - 0% Cluster 3
- clusters may be associated with varying aggressiveness

Investigative work

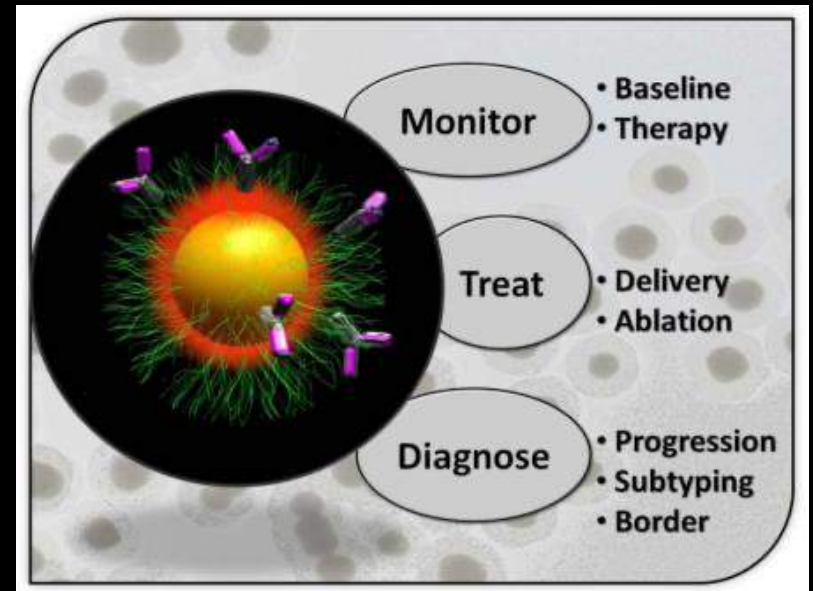
- Non-Invasive Assessment of Breast Cancer Molecular Subtypes with Multiparametric Magnetic Resonance Imaging Radiomics
Leithner D, et al. *J Clin Med*. 2020 Jun 14;9(6):1853
- Radiomic Signatures Derived from DWI for the Assessment of Breast Cancer Receptor Status and Molecular Subtypes
Leithner D, et al. *Mol Imaging Biol*2020; 22(2): 453–461
- MRI Radiomic Features: Association with Disease-Free Survival in Patients with Triple-Negative Breast Cancer
Kim S, et al. *Sci Rep*. 2020 Feb 28;10(1):3750
- Dual-Modality Surface-Enhanced Resonance Raman Scattering and Multispectral Optoacoustic Tomography Nanoparticle Approach for Brain Tumor Delineation
Small ... Kircher. 2018 Jun;14(23) e1800740. doi: 10.1002/sml.201800740

Molecular imaging and theranostics

- Nanoparticles offer unique diagnostic and therapeutic possibilities
- Theranostics = technology capable of diagnosis & treatment
- Sub-micron particles → Theranostic Nanomedicine
- Nanoparticles FDA approved for clinical use for ~2 decades
- Applications remain investigational

Theranostics

- Ideal nanoparticle
 - Accumulates in diseased tissue
 - Reports local conditions
 - Delivers therapy
 - Biodegrades safely



Jokerst, Gambhir. Molecular imaging with Theranostic Nanoparticles. *Acc Chem Res* 2011;44(10)1050-1060

A moment to honor two brilliant scientists

 **Stanford**
MEDICINE | Nuclear Medicine and Molecular Imaging
Radiology



In Loving Memory of
Sanjiv Sam Gambhir, MD, PhD

November 23, 1962 - July 18, 2020



Moritz F. Kircher, MD, PhD
Director, Molecular Cancer Imaging Facility
Dana-Farber Cancer Institute &
Harvard Medical School

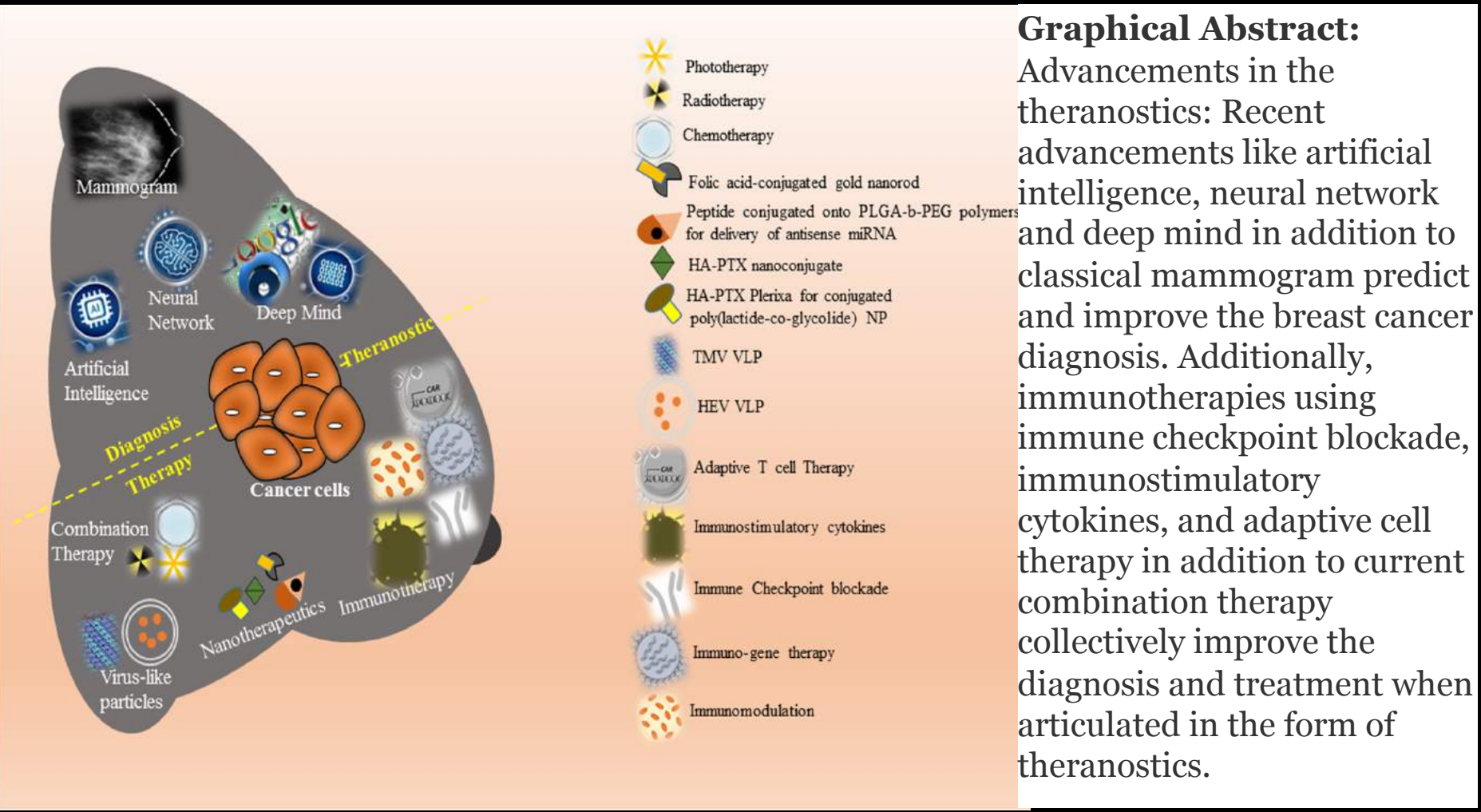
Imaging breast cancer using a dual-ligand nanochain particle

Covarrubias G. PLoS One. 2018 Oct 18;13(10):e0204296

- In vivo performance of iron oxide nanoparticle
 - targeting and imaging of aggressive breast tumors in mice
 - a multi-component nanochain, 3-5 iron oxide nanoparticles
 - two ligands targeting two upregulated biomarkers on tumor endothelium, P-selectin and fibronectin
 - Showed improved tumor deposition
 - Single-ligand nanochain had ~2.5-fold higher intratumoral deposition than a spherical nanoparticle
 - **dual-ligand nanochain showed detectable MR signals**
 - Dual-ligand nanochains highly visible on 7T MRI within 3h after injection in two different animal models of breast cancer

Recent advances in nanotheranostics for triple negative breast cancer treatment

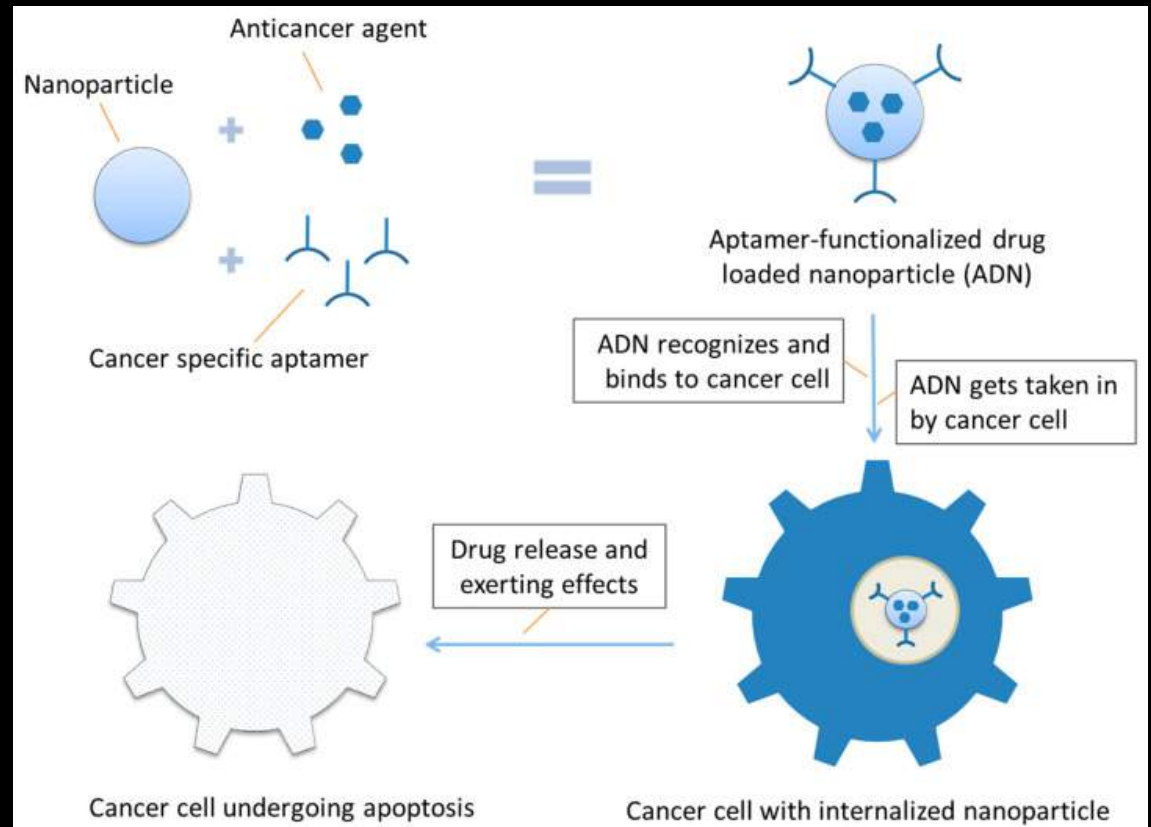
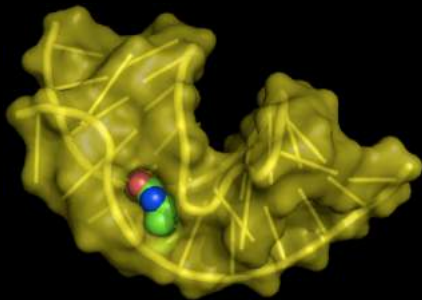
Thakur & Kutty. Journal of Experimental & Clinical Cancer Research 2019



Aptamer-Functionalized Nanoparticles in Targeted Delivery and Cancer Therapy

Fu Z, et al. Int J Mol Sci. 2020 Nov 30;21(23):9123

- Nanoparticles combined with aptamers
- Aptamers are single stranded RNA or DNA oligonucleotides that bind avidly to specific molecular targets



Anti-EGF Receptor Aptamer-Guided Co-Delivery of Anti-Cancer siRNAs and Quantum Dots for Theranostics of **TNBC**

Kim MW, et al. Theranostics. 2019 Jan 25;9(3):837-852

- Results

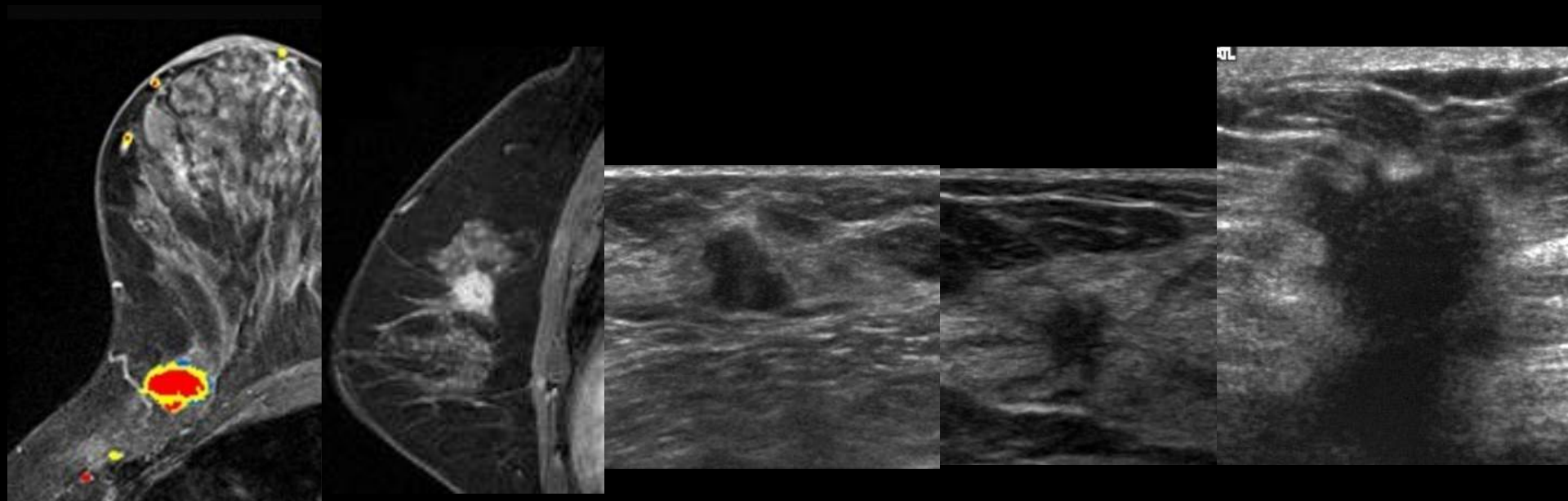
- Both types of EGFR-targeting QLs showed enhanced delivery to target cancer cells, resulting in more effective gene silencing and enhanced tumor imaging compared to non-targeting control QLs. Moreover, combinatorial therapy with Bcl-2 and PKC- ι siRNAs loaded into the anti-EGFR QLs was remarkably effective in inhibiting tumor growth and metastasis

- Conclusions

- In general, the aptamo-QLs showed competitive *in vivo* delivery and therapeutic efficacy compared to immuno-QLs under the same experimental conditions. Our results show that the anti-EGFR aptamer-guided lipid carriers may be a potential theranostic delivery vehicle for RNA interference and fluorescence imaging of TNBCs.

In summary

- Most TNBC will have the typical cancer appearance
- BUT they can mimic "benign" masses
- Especially in BRCA 1 or 2 women
- AI based radiomics may show imaging phenotypes reflecting growth patterns of TNBC subtypes
- Nanoparticle imaging may identify specific targets for Dx & Tx



Summary

- Goals should be to
- Identify genomic predictors in pt populations
- Clinical and imaging characteristics of breast cancer subtypes
- Provide personalized risk assessment



- Earlier detection and treatment





thank you