Learning objectives

- How imaging markers are used in the neoadjuvant treatment trial
- MRI markers for the prediction to treatment response and recurrence-free survival
- Use of PET molecular imaging markers to inform assess early treatment response and drug selection

Neoadjuvant chemotherapy (NAC) in breast cancer

National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol B-18 and B-27

- No difference in disease-free survival or overall survival in patients receiving neoadjuvant chemotherapy with AC or AC + taxane compared to those receiving adjuvant therapy

Clinical Trial Model

- Treatment interval: initial neoadjuvant chemotherapy followed by surgery and adjuvant chemotherapy
- Assess the ability of imaging biomarkers to predict treatment response
- Identify new tools for prognostic assessment
- Accelerate new drug development

Timeline

- Years (5-20)
- Months

- Neoadjuvant
- Primary tumor
- Response
Contrast-enhanced MR Imaging

Functional tumor volume

- Functional tumor volume (FTV) has been used to monitor treatment response in breast cancer patients.
- Using a three-time point acquisition strategy ($t_0$, $t_1$, and $t_2$) at the time of contrast injection, a signal-enhancement-ratio (SER) map is generated.
- FTV is the sum of all the voxels meeting the enhancement threshold in the SER map.

**I-SPY 1/ACRIN 6657**

PI: Esserman and Hylton

- pCR and RCB

**I-SPY 1/ACRIN 6657 Key Findings**

- MRI volume (FTV) was a strong predictor of pCR and RCB at all time points.
- FTV was a stronger predictor of recurrence free survival (RFS) than pCR.
- FTV2 had the highest overall C statistic when combined with RCB.
- FTV (highest quartile cut point) discriminate differences in survival outcomes and the optimal timing of MRI imaging measurement differ by subtype.

**I-SPY 2 TRIAL**

PI: Esserman & Berry

- pCR + pathologic complete response
- RCB + residual cancer burden

Key Findings:

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I-SPY 2 is a response-agnostic phase II trial testing novel agents for breast cancer.
- Drugs "graduate" from I-SPY 2 when they reach a Bayesian predictive probability of achieving 85% success in a subsequent 300-patient phase III trial.
- MRI response is used to adjust patient randomization ratio and to estimate the predictive probabilities.

>3000 patients registered
>1500 patients completed surgery
14 agent combinations
7 drugs graduated
Dedicated breast PET (Db-PET)

- Imaging of the primary breast tumor during treatment can provide critical prognostic and predictive information
- High sensitivity of Db-PET can detect tumors at low dose of radiotracers (≤5 mCi) allowing longitudinal studies with minimum radiation exposure
- High-resolution imaging capability from dedicated breast PET, we will be able to capture early treatment response as well as high quality imaging features that are of prognostic value

Initial experience with FDG-dbPET

- Patient characteristics
  - 32 yo female BRCA 1 carrier with 3 biopsy confirmed lesions
  - 2 lesions in the right breast
    - ER+/PR-, HER2-
    - Triple negative (TN)
  - 1 lesion in the left breast
    - Triple negative (TN)
- A dose of 5 mCi of FDG was administered and the patients was imaged in the prone position at 45 min post-injection

Initial experience with DbPET

- 32 yo female BRCA 1 carrier with 2 lesions in the right and 1 in the left
- Overall FTV
  - 73.2 cc
  - SUV<sub>max</sub> TN: 19.5 ER+: 18.1
- Overall FTV
  - 88.5 cc
  - SUV<sub>max</sub> TN: 15.3

MRI examinations at later time points showed a more dramatic response to therapy in the TN tumor and near complete pathologic response was documented at mastectomy.

Jones et al., Clinical Breast Cancer, 2017
### Results

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Age (mean [range])</th>
<th>Subtype</th>
<th>Ki67 (mean [range])</th>
<th>RCB</th>
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<td>HR+/HER2</td>
<td>47.8 (17.5-80.0)</td>
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<tr>
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<td>TN</td>
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</table>

### Early detection of treatment response

![PET images showing treatment response](image)

**FES for imaging ER+ breast cancers**

- ~70% breast cancers are ER+
- FES was developed for PET imaging of ER status
- Earlier clinical studies show that FES uptake in tumor correlates with the level of ER expression in biopsy samples and is predictive to endocrine treatment response
- These initial findings substantiate the utility of FES-PET as an in vivo assay to select appropriate treatment for ER+ patients

**Whole body FES-PET of ER+ breast cancers**

- 18F-FES PET imaging of 33 patients
  - Equivocal lesions
  - ER status
  - Origin
  - Progression led to therapy change

**[18F]Fluoroestradiol (FES)**

- Estradiol A form of estrogen

**FDA APPROVED**

**Bone scan FES-PET**

[Image of bone scan with FES-PET]
FES-PET Imaging of ER+ Breast Cancer
Response to tamoxifen, fulvestrant, aromatase inhibitor (AI)

- Patients with biopsy confirmed ER+ (>90%) and HER2- breast cancers were imaged with dbPET and standard breast dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI)
- A dose of 5 mCi of FES was administered and patients were imaged in the prone position at 45 min post-injection

Results
- To date, we have imaged 14 breast cancer patients with >90% ER+ and HER2- using [18F]FES-dbPET
- Patient age ranged from 23 to 76, with a range of Ki67 from 1 to 30%
- While all patients have >90% ER+, they exhibit different imaging patterns

Initial experience of FES-dbPET imaging
- Patient A: Diffused FES uptake pattern in ILC
- Patient B: Well circumscribed pattern in IDC
- Patient D: No FES uptake due to prior treatment with tamoxifen

FES-dbPET Imaging of patients >90% ER+

A
SUVmax = 15.83

B
SUVmax = 5.02
Summary

- MRI FTV is a reliable marker to monitor neoadjuvant treatment response
- The use of FDG-dbPET along with breast MRI may present an opportunity to guide earlier treatment redirection
- FES-dbPET has varying FES uptake pattern in ILC and IDC ER+ breast cancer diseases
- Baseline FES uptake may inform treatment planning for ER+ breast cancer. Treatment induced change of FES uptake can be used to inform response and subsequent treatment

Future directions

- In addition to FTV, MRI background parenchymal enhancement and apparent diffusion coefficient from diffusion weighted imaging are currently being explored as multivariate predictors
- Compare FDG-dbPET with MRI for assessing the early detection of treatment response
- FES uptake to inform treatment selection in ER+ breast cancers. FES-dbPET will also be used assess the efficacy of new selective ER degrader (SERD)
- Invasive lobular carcinoma is mostly ER+, we believe that FES-dbPET uptake will provide important information of this breast cancer subtype
- The high spatial resolution of dbPET and MRI may afford high quality radiometric features to correlate with molecular signatures to inform tumor biology