The Utility & Limitations of Imaging in the Management of Gynecologic Malignancy

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University of Oklahoma
Disclosures

None
Objectives

• Overview of Current Imaging Modalities
  o Current Limitations in Imaging
  o Unmet Clinical Needs

• Review the Role of Emerging Imaging Technology and Potential Application to Gynecologic Malignancy
Brief Overview of the Gynecologic Malignancies
# Lifetime Probability of Developing Cancer, Women, US, 2004-2006*

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<td>All sites†</td>
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† All Sites exclude basal and squamous cell skin cancers and in situ cancers except urinary bladder.
‡ Includes invasive and in situ cancer cases
§ Statistic for white women.

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Cancer of the Lower Genital Tract

- **Vulvar Cancer**
  - Incidence – 4700 cases/year
  - Mortality – 990 deaths/year

Cancer of the Lower Genital Tract

• Vulvar Cancer
• Vaginal Cancer
  o Incidence – 2890 cases/year
  o Mortality – 840 deaths/year

Cancer of the Lower Genital Tract

- Vulvar Cancer
- Vaginal Cancer
- **Cancer of the Uterine Cervix**
  - Incidence:
    - Worldwide – 530,000 cases/year
    - 3rd leading cause of female cancer worldwide
    - Developing nations carry the burden
    - USA – 12,304 cases/year
  - Mortality
    - Worldwide – 275,000 deaths/year
    - 8% of female cancer death
    - 90% in developing countries
    - USA – 4030 deaths/year

Cancer of the Uterine Corpus

- **Histology**
  - Endometrial - 98%
    - Adenocarcinoma arising from glandular tissue
  - Sarcoma - 2%
    - Arise from mesenchymal tissue of uterus
      - Leiomyosarcoma
      - Endometrial Sarcomas
        - Endometrial stromal sarcoma
        - Adenosarcoma
Cancer of the Uterine Corpus

- Incidence – 49,560 cases/year
  - 98% of uterine corpus cancer - ENDOMETRIAL
    - Increasing 1% per year (2000 - 2010)
    - Prevalence > 600,000 women

- Mortality – 8190 deaths/year
Histologic Division of Ovarian Cancer

- **Epithelial tumors – 85%**
  - Coelomic epithelial lining of the ovary – adenocarcinoma
  - Serous predominant histology
  - Late stage at diagnosis – 80%

- **Germ cell – 10%**
  - Germinal epithelium within the ovary
  - Young patients
  - Early stage at diagnosis is the norm

- **Sex cord-stromal – 5%**
  - Mesenchymal tissue of the ovary
  - Early stage at diagnosis
  - Delayed time to recurrence
Cancer of the Ovary

- Incidence – 22,240 cases/year
- Mortality – 14,030 deaths/year
  - 5th leading cause of cancer death in USA
The Role of Standard Imaging in the Lower Genital Tract
Lower Genital Tract

- Vulva, vagina & cervix
  - Staging & Treatment Planning

LIMITED USE OF SURGERY IN THESE DISEASE SITES
Lower Genital Tract

- Vulva, vagina & cervix
  - Staging & Treatment Planning

**TREATMENT = CLINICAL EXAM + IMAGING RESULTS**
Lower Genital Tract

- Vulva, vagina & cervix
  - Staging & Treatment Planning

\[ \text{TREATMENT = CLINICAL EXAM + IMAGING RESULTS} \]

\[ +/- \text{ LYMPH NODE ASSESSMENT} \]
Vulvar cancer: a surgically staged disease

Table 1
Carcinoma of the vulva.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
</table>
| Stage I | Tumor confined to the vulva  
IA | Lesions ≤2 cm in size, confined to the vulva or perineum and with stromal invasion ≤1.0 mm*, no nodal metastasis  
IB | Lesions >2 cm in size or with stromal invasion >1.0 mm*, confined to the vulva or perineum, with negative nodes |
| Stage II | Tumor of any size with extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with negative nodes |
| Stage III | Tumor of any size with or without extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus) with positive inguino-femoral lymph nodes  
IIIA | (i) With 1 lymph node metastasis (≥5 mm), or  
(ii) 1–2 lymph node metastasis(es) (<5 mm)  
IIIB | (i) With 2 or more lymph node metastases (≥5 mm), or  
(ii) 3 or more lymph node metastases (<5 mm)  
IIIC | With positive nodes with extracapsular spread |
| Stage IV | Tumor invades other regional (2/3 upper urethra, 2/3 upper vagina), or distant structures  
IVA | Tumor invades any of the following:  
(i) upper urethral and/or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bone, or  
(ii) fixed or ulcerated inguino-femoral lymph nodes  
IVB | Any distant metastasis including pelvic lymph nodes |

*The depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.
Anatomy of the Groin

- Superficial inguinal nodes
- Inguinal ligament
- Iliopsoas m.
- Femoral lymph nodes
- Femoral v. and a.
- Sartorius m.
- Femoral n.
- Fossa ovalis
- Pectineus m.
- Adductor longus m.

Skin and subcutaneous tissues
Fascia lata

Transversalis fascia
The Clinically Staged Malignancies of the Lower Genital Tract

Figure 1. Staging of uterine cervix carcinoma according to FIGO(3).

**TABLE 1**

<table>
<thead>
<tr>
<th>FIGO staging system for cervical cancer.</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIa</td>
</tr>
<tr>
<td>IIIa1</td>
</tr>
<tr>
<td>IIIa2</td>
</tr>
<tr>
<td>IIIb</td>
</tr>
<tr>
<td>IIIb1</td>
</tr>
<tr>
<td>IIIb2</td>
</tr>
<tr>
<td>IVa</td>
</tr>
<tr>
<td>IVa1</td>
</tr>
<tr>
<td>IVa2</td>
</tr>
<tr>
<td>IVb</td>
</tr>
<tr>
<td>IVb1</td>
</tr>
<tr>
<td>IVb2</td>
</tr>
<tr>
<td>IVc</td>
</tr>
<tr>
<td>IVc1</td>
</tr>
<tr>
<td>IVc2</td>
</tr>
</tbody>
</table>

FIGO = International Federation of Gynecology and Obstetrics.
## Vagina Staging Form

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Stage Category Definitions</th>
<th>Pathologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extent of disease before any treatment</td>
<td></td>
<td>Extent of disease during and from surgery</td>
</tr>
<tr>
<td>TNM Category</td>
<td>FIGO Stage</td>
<td>TNM Category</td>
</tr>
<tr>
<td>T0</td>
<td>Primary Tumor (T)</td>
<td>T0</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
<td>Tis</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor confined to vagina</td>
<td>T1</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades paravaginal tissues but not to pelvic wall</td>
<td>T2</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor extends to pelvic wall**</td>
<td>T3</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invades mucosa of the bladder or rectum and/or extends beyond the true pelvis (bullous edema is not sufficient evidence to classify a tumor as T4)</td>
<td>T4</td>
</tr>
</tbody>
</table>

*FIGO staging no longer includes Stage 0 (Tis).

**Pelvic wall is defined as muscle, fascia, neurovascular structures, or skeletal portions of the bony pelvis.

### Regional Lymph Nodes (N)

<table>
<thead>
<tr>
<th>TNM Category</th>
<th>FIGO Stage</th>
<th>Regional Lymph Nodes cannot be assessed</th>
<th>No regional lymph node metastasis</th>
<th>Pelvic or inguinal lymph node metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>N0</td>
<td>Regional lymph nodes cannot be assessed</td>
<td>No regional lymph node metastasis</td>
<td>Pelvic or inguinal lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>III</td>
<td>Regional lymph nodes cannot be assessed</td>
<td>No regional lymph node metastasis</td>
<td>Pelvic or inguinal lymph node metastasis</td>
</tr>
</tbody>
</table>

### Distant Metastasis (M)

<table>
<thead>
<tr>
<th>TNM Category</th>
<th>FIGO Stage</th>
<th>Distant Metastasis (no pathologic M0; use clinical M to complete stage group)</th>
<th>Distant Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>IVB</td>
<td>No distant metastasis (no pathologic M0; use clinical M to complete stage group)</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>IVB</td>
<td>No distant metastasis (no pathologic M0; use clinical M to complete stage group)</td>
<td>Distant metastasis</td>
</tr>
</tbody>
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CT Imaging: Lower Genital Tract

- **Vulva**
  - Staging & Treatment Planning
    - CT
      - Lymph node assessment
        - Grossly positive - >90%
        - Grossly negative – 30%

- **Cervix (Vagina)**
  - Staging & Treatment Planning
    - CT
      - Parametria – 75% accuracy
      - Lymph node metastasis
        - Grossly positive – 80-85%
        - Grossly negative – 20-30%
MRI: Lower Genital Tract

- Vulva
  - Staging & Treatment Planning
    - MRI – not validated

- Cervix
  - Staging & Treatment Planning
    - MRI
      - Parametria – 90%
      - Lymph nodes (similar to CT)
        - Grossly positive – 90%
        - Grossly negative – 20-30%
ACRIN 6651:

MRI & CT Evaluation in Early Cervical Cancer

- MRI Superior
  - Primary tumor
  - Parametrial invasion
  - Prediction of nodal metastases

- CT Concerns
  - More interobserver variability

Neither method reliable in predicting cervical stromal invasion
Correlating Clinical Staging & MRI

Table 1  Correlation between FIGO staging of uterine cervix cancer and MRI findings\textsuperscript{(17)}.

<table>
<thead>
<tr>
<th>Stage</th>
<th>MRI T2-weighted sequence</th>
</tr>
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<tbody>
<tr>
<td>Ia Microinvasor</td>
<td>No tumor evidence</td>
</tr>
<tr>
<td>Ib Invasive, confined to the cervix</td>
<td>Hyperintense tumor on T2-weighted sequence in contrast with hypointense signal from cervical stroma</td>
</tr>
<tr>
<td>Ib\textsubscript{1} Clinically visible lesion $\leq$ 4 cm</td>
<td>Tumor partially or completely replacing the hypointense cervical stroma, not surpassing the parametrial interface represented by a hypointense halo</td>
</tr>
<tr>
<td>Ib\textsubscript{2} Clinically visible lesion $&gt;$ 4 cm</td>
<td>Segmental interruption of hypointense signal on the upper third of the vaginal wall</td>
</tr>
<tr>
<td>IIa Tumor invades the upper vaginal third, but does not affect the lower vaginal third</td>
<td>Hyperintense tumor interrupting hypointense halo of the interface between cervical stroma and parametrium</td>
</tr>
<tr>
<td>IIb Tumor invades the parametrium, but not the pelvic wall neither the lower vaginal third</td>
<td>Segmental interruption of the hypointense signal of the lower vaginal third</td>
</tr>
<tr>
<td>IIIa Involvement of the lower vaginal third, without affecting the pelvic wall</td>
<td>Tumor extending to the musculature (internal obturator muscle, piriform muscle or levator ani muscle) or causing hydroureter</td>
</tr>
<tr>
<td>IIIb Pelvic wall involvement or hydrencephrosis</td>
<td>Loss of hypointense signal of the internal wall (mucosa) of the bladder or rectum</td>
</tr>
<tr>
<td>IVa Tumor invades the bladder or rectum mucosa</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>IVb Distant metastasis</td>
<td>Distant metastasis</td>
</tr>
</tbody>
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Ultrasound : Lower Genital Tract

- Vulva
  - Staging & Treatment Planning
    - Ultrasound – no clinical utility

- Cervix
  - Staging & Treatment Planning
    - Ultrasound
      - Limited role in assessment
      - Fertility preservation
Disease Surveillance in Lower Genital Tract Malignancy

- Post-Treatment Surveillance
  - CT
  - MRI
The Role of Standard Imaging in the Uterine Malignancy
Standard Imaging: Uterine Corpus

- Uterine Corpus
  - Staging & Treatment Planning

**SURGICALLY STAGED DISEASE**

**CURRENT STANDARD: TAH/BSO/PPALND**
<table>
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<th>Stage</th>
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<td>Tumor contained to the corpus uteri</td>
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<tr>
<td>IA</td>
<td>No or less than half myometrial invasion</td>
</tr>
<tr>
<td>IB</td>
<td>Invasion equal to or more than half of the myometrium</td>
</tr>
<tr>
<td>II</td>
<td>Tumor invades the cervical stroma but does not extend beyond the uterus</td>
</tr>
<tr>
<td>III</td>
<td>Local and/or regional spread of tumor</td>
</tr>
<tr>
<td>IIIA</td>
<td>Tumor invades the serosa of the corpus uteri and/or adnexas</td>
</tr>
<tr>
<td>IIIB</td>
<td>Vaginal and/or parametrial involvement</td>
</tr>
<tr>
<td>IIIC</td>
<td>Metastases to pelvis and/or para-aortic lymph nodes</td>
</tr>
<tr>
<td>IIIC1</td>
<td>Positive pelvic nodes</td>
</tr>
<tr>
<td>IIIC2</td>
<td>Positive para-aortic lymph nodes with or without positive pelvic lymph nodes</td>
</tr>
<tr>
<td>IV</td>
<td>Tumor invades bladder and/or bowel mucosa and/or distant metastases</td>
</tr>
<tr>
<td>IVA</td>
<td>Tumor invasion of bladder and/or bowel mucosa</td>
</tr>
<tr>
<td>IVB</td>
<td>Disant metastases, including intra-abdominal metastases and or inguinal lymph nodes</td>
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FIGO = International Federation of Gynecology and Obstetrics

* Includes grades 1, 2, or 3

* Endocervical glandular involvement only should be considered as stage I and no longer as stage II.

* Positive cytology has to be reported separately without changing the stage.
Retroperitoneal Anatomy
CT: Uterine Corpus

- Uterine Corpus
  - Staging & Treatment Planning
    - CT (contrast enhanced)
      - Accuracy – 86%
      - Utility
        - Lymph node metastases
        - Parenchymal solid organ
        - Ascites
MRI: Uterine Corpus

- Uterine Corpus
  - Staging & Treatment Planning
    - MRI
      - Accuracy – 84-94%
      - Myometrial Invasion
        - Dynamic contrast-enhanced T1 & T2 weighted images
        - Accuracy – 85-91%
        - Fertility Preservation
Ultrasound : Uterine Corpus

• Uterine Corpus
  o Staging & Treatment Planning
    • Ultrasound
      o Myometrial Invasion
        • Accuracy – 75% (68-83)
      o Cevical Stromal Invasion
        • Accuracy – 85% (60-88)

Fischerova et al, 2013
The Role of Imaging in the Ovarian Malignancy
Cancer of the Ovary & Peritoneum

- Ovarian Cancer

SURGICALLY STAGED DISEASE
Cancer of the Ovary & Peritoneum

- Ovarian Cancer

**ROLE OF SURGERY**

1. Staging
2. Therapy
Surgical Cytoreduction

- **Evolving definition**
  - No gross residual disease → 1 cm → 2 cm
  - Survival benefit - ≤ 22 months

- **Rates of “Optimal” resection**
  - 35% (20-85%)
    - 45-50% in experienced centers
  - Predicting who will benefit - KEY
Advanced Ovarian Cancer Surgery

- **Aggressive Surgery**
  - Bowel resection – 15%
  - Splenectomy – 15%
  - Radical peritoneal resection

- **Drawbacks of Surgery**
  - Complications
  - Chemotherapy delays
Primary Cytoreductive Surgery (CRS)

- Meta-analysis: 53 studies (1989-98)
  - Stage III/IV
  - 6885 patients

- Results
  - Expert centers have high optimal rates
  - Optimal = 22 month survival advantage
  - Each 10\% \textbf{in cytoreduction} = 5.5\% \textbf{in survival}

Bristow, J Clin Oncol 20:1248, 2002
Impact of Optimal CRS

Chi Gynecol Oncol (2006) 103:559
GCIG Consensus Recommendations: Surgery in Advanced Ovarian Cancer

1. **Up-front maximal surgical effort** at cytoreduction with the goal of **no residual disease** should be undertaken.

2. Surgery should be performed by an appropriately trained surgeon with experience in ovarian cancer management.
Standard Imaging: Ovary & Peritoneum

- Ovary, Fallopian Tube & Peritoneum
  - Screening
    - No effective imaging
CT: Ovary & Peritoneum

- Ovary, Fallopian Tube & Peritoneum
  - Staging & Treatment Planning
    - CT
      - Best resolution
      - Current standard

Contrast enhanced CT: surface implant in intersegmental tissue of liver – Qayyum et al 2005

Contrast-enhanced CT: gastrohepatic ligament & superficial liver implants – Qayyum et al 2005
MRI: Ovary & Peritoneum

- Ovary, Fallopian Tube & Peritoneum
  - Staging & Treatment Planning
    - MRI
      - Movement dependent
      - Improved solid organ characterization

T2 weighted image: gastrohepatic ligament implant – Qayyum et al 2005

Delayed gadolinium enhanced MRI: subdiaphragmatic tumor - Low et al 2009
Ultrasound: Ovary & Peritoneum

- Ovary, Fallopian Tube & Peritoneum
  - Staging & Treatment Planning
    - Pelvic ultrasound
      - Key Role: mass characterization
      - Limited role in predication of stage
Predicting Inoperability in EOC

**CT**
- 70% accurate (Axtell et al. 2007)
- Models remain UNRELIABLE (Ibeanu & Bristow 2010)
  - Diffuse peritoneal thickening
  - Ascites

**MRI**
- Conventional MRI = CT (Qayyum et al. 2005)
  - Gadolinium contrast enhanced
Where Are We Continuing To Fall Short?
A Gyn Oncologist’s Opinion
Lower Genital Tract

- What is the Gold Standard?
  - Imaging vs TISSUE
Lower Genital Tract

- What is the Gold Standard?
- Inflammation ≠ Disease
  - Nodal Enlargement
  - Adjacent organ involvement
Lower Genital Tract

• What is the Gold Standard?
• Inflammation ≠ Disease
• Physiologic GI/GU contrast or nuclear imaging agents
Uterine Corpus

- Surgical Staging – A Concept of the Past?
  - Clinical trials question role of lymphadenectomy
    - ASTEC
  - Radiographic prediction of extra-uterine disease may become critical
Uterine Corpus

- Surgical Staging – A Concept of the Past?
- Younger patients (increasing obesity)
  - Fertility conservation
    - When is it safe?
    - What is the optimal imaging strategy:
      - Myometrial Invasion
Ovary & Peritoneum

• Screening Options
  o No identifiable cancer precursor
  o No improvement in stage at diagnosis
  o No improvement in disease related survival
Ovary & Peritoneum

- Screening Options
- Diagnosis of cancer
Ovary & Peritoneum

- Screening Options
- Diagnosis of Cancer
- RESCTABILITY, RESECTABILITY, RESECTABILITY...
Resectability in Person
Overall Cancer Imaging

• **Surrogate Outcomes Measure**
  o Validated
  o Reproducible
  o Cost Effective

• **Assessment of Drug Therapy**
  o Biologics ≠ Cytotoxics
Combating Our Current Shortcomings
GCIG Statement on Imaging

• GCIG Recommendations for Imaging in Clinical Trials
  o Dynamic contrast-enhanced (perfusion) CT
  o Dynamic contrast-enhanced MRI
  o Diffusion weighted MRI
  o FDG-PET/CT and FDG-PET/MRI

• Functional Imaging as a Clinical Trial Endpoint
Lower Genital Tract

- Functional Imaging Modalities
  - $^{18}$FDG-PET/CT
  - DWI-MRI
  - DCE imaging
FDG-PET: Lower Genital Tract

- Vulva
- Cervix (Vagina)
  - FDG-PET CT (Grigsby et al)
    - Lymph nodes
      - Grossly positive – 99%
DWI: Lower Genital Tract

- Cervix
FDG-PET: Uterine Corpus

- Uterine Corpus
  - Staging & Treatment Planning – Nodal Assessment
    - PET/CT
      - Accuracy – 83%
      - PPV – 28% / NPV - 94%
DWI: Uterine Corpus

- Uterine Corpus
  - Staging & Treatment Planning – Nodal Assessment
    - Comparable to PET/CT
    - EXCEPT – fertility preservation
FDG-PET: Ovary & Peritoneum

• Epithelial Ovarian/Peritoneal Cancer
  o Staging & Treatment Planning
  o Disease surveillance
    • Small, diffuse implants – not well characterized with anatomic imaging
DWI: Ovary & Peritoneum

- Epithelial Ovarian/Peritoneal Cancer
  - Staging & Treatment Planning
    - Predicting Resectability
Active ACRIN Trials

- **ACRIN 6671/GOG233**: Utility of PET/CT scanning prior to retroperitoneal lymphadenectomy in locoregionally advanced cervix cancer OR endometrial cancer that is high grade or involves the uterine cervix
  - Iron oxide (ferumoxtan) MRI for nodal staging
  - Closed early due to supply
Retroperitoneal Lymphadenectomy Pathology Revealing Microscopic Para-Aortic Nodal Metastasis

Primary Cervical Tumor
Active ACRIN Trials

- ACRIN 6651
- ACRIN 6671/GOG233
- **ACRIN 6682**: Phase II trial of $^{64}$Cu-ATSM PET/CT in cervical cancer – actively accruing patients
  - Focus – Tumor Necrosis
  - ?Predictor for poorer response?
ACRIN 6682 - $^{64}$Cu-ATSM in Necrotic Tumor

FDG-PET/CT

$^{64}$Cu-ATSM
Active ACRIN Trials

- ACRIN 6651
- ACRIN 6671/GOG233
- ACRIN 6682:

**ACRIN 6695/GOG262:** Perfusion CT imaging to evaluate treatment response in advanced ovarian cancer
  - Perfusion as a predictor of disease response
  - Perfusion as a predictor for survival
  - Changes in perfusion in response to antiangiogenic therapy
Future Clinical Trial Directions

- Validating Tissue Biomarkers with Functional Imaging
  - Dynamic Contrast-Enhanced Imaging (CT & MRI) – ACRIN 6695
    - Tumor vessel density
    - Microvessel counts
    - VEGF
  - Diffusion Weighted MRI Imaging
    - Ki-67 proliferation index
    - Cellularity index (tumor cells/hpf)
    - EGFR
    - CD31 expression
Molecular Imaging

- Fusing patient-specific and disease-specific molecular targets with traditional anatomical imaging
Molecular Imaging

• Fusing patient-specific and disease-specific molecular targets with traditional anatomical imaging
  o Is there a target?
Molecular Imaging

- Is there a target? **YES**
  - Cancer Specific Targets
    - **Nuclear**
      - 18FDG
      - 18Fluorothymidine
      - Arcitumomab
      - Satumomab
      - Bombesin
      - Estrogen receptor ligands
      - Folate receptor ligands
      - Annexin
    - **MRI**
      - Integrins

Jaffer et al JAMA 2005
Molecular Imaging

- Fusing patient-specific and disease-specific molecular targets with traditional anatomical imaging
  - Is there a target?
  - Is there a ligand that will bind the target?
Molecular Imaging

- Fusing patient-specific and disease-specific molecular targets with traditional anatomical imaging
  - Is there a target?
  - Is there a ligand that will bind the target?
  - What is the appropriate imaging system for the disease?
    - Nuclear (SPECT/PET)
    - MRI/CT platform
Molecular Imaging

- Fusing patient-specific and disease-specific molecular targets with traditional anatomical imaging
  - Is there a target?
  - Is there a ligand that will bind the target?
  - What is the appropriate imaging system for the disease?
  - Can the synthesized molecular target be detected by the imaging system?
Theoretical Benefits & Molecular Imaging

1. Earlier cancer diagnosis
   • Subcentimeter disease
2. Improved imaging specificity
   • Targeted biomarkers
3. Tumor response to drug therapy
   • Molecular readouts of drug activity
4. Improved understanding of disease development and persistence
   • Biologic modeling for cellular and metabolomic events
     o Angiogenesis
     o Apoptosis
     o Stem cell trafficking
     o Thrombosis
References


