PET/CT and PET/MR in Gynecological Malignancies

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FDG PET/CT in gynecology:

1. **Physiological uptake**
2. Ovarian cancer
3. Cervical carcinoma
4. Endometrial carcinoma
FDG – physiologic uptake:

Patient with Melanoma in CR since 2 years: FDG activity in the uterine cave and right adnex
=> Ovulation phase
FDG – physiologic uptake:

56 yo Breast cancer since 8 years after several antihormonal and chemo therapies:

- Focal FDG activity in the Liver
  ⇒ Liver Metastasis
- Focal activity in both ovaries
  \[(\text{SUV}_{\text{max}} 3.5)\]
  ⇒ Bilateral ovarian metastasis
FDG – physiologic uptake:

Hypothesis:
I) Increased uptake in the dominant follicle due to elevated metabolism
II) Inflammatory reaction after ovulation
Physiological $^{18}$F-FDG uptake in the ovaries and uterus of healthy female volunteers

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¹ Hamamatsu Medical Imaging Center, Hamamatsu Medical Photonics Foundation, Hamakita, Shizuoka, Japan

PET & MR in 133 healthy volunteers: 78 pre- and 55 postmenopausal

I) Ovarian uptake in late follicular - early luteal phase (day 10-18) in 26 of 32 patients (81%) SUV $3.9 \pm 0.7$, range 2.6–5.2
   Unilateral uptake 23/26, 88%

II) Endometrial uptake during day 10-18 in 18/32, 56% SUV $3.3 \pm 0.3$, 2.8-4.0

III) Endometrial uptake during menstruation SUV $4.6 \pm 1.0$, 3.5-6.1

IV) No physiologic uptake in all 55 postmenopausal women
   (except FDG active uterine myomas)
FDG – physiologic uptake:

Same patient as in case 1: one year later (CR since 3 years):

FDG activity only in the uterine cave with markedly increased SUV

=> During menses
FDG – physiologic uptake:

Side note:
Vaginal tampons should be removed or changed after voiding

The high uptake is due to urinary contamination, high spill over could obscure surrounding structures
FDG – possible interference:

25 y.o. woman
breast cancer:

FDG activity in the cervix,
SUV$_{\text{max}}$ 4.3

Cervical cancer
FDG – physiologic uptake?:

51 y.o. woman
Melanoma with mediastinal and pulmonary metastasis:

FDG activity right adnex
$SUV_{\text{max}}$ 7.2
And milde activity in the uterine cave ($SUV_{\text{max}}$ 3.2)

Transvaginal sonographie:
Bleeding into corpus luteum cyst
FDG – physiologic uptake?:

PET/CT of the female genital tract
FDG PET/CT in gynecology:

1. Physiological uptake
2. Ovarian cancer
3. Cervical carcinoma
4. Endometrial carcinoma
Histology:

- WHO classification of surface epithelial-stromal tumors (>90%)
  - Papillary serous tumors (42%)
  - Mucinous tumors
  - Endometrioid tumors
  - Clear-cell tumors
  - Transitional cell tumors (Brenner tumor)
  - Squamous cell tumors
  - Mixed epithelial tumors
  - Undifferentiated carcinoma

- Germ cell tumors (Teratoma, gestational trophoblastic tumors)
Adneocarcinomas:

- Median age over 60 years
- Lifetime risk 1 to 70
- Risk factors:
  - Family history of ovarian and breast cancer
  - Inherited mutation of BRCA1 or BRCA2

- USA 2014 estimates:
  - new cases per year: 22’000
  - Cancer death per year: 14’000
For all ovarian carcinomas surgery is the first step.  
-> cytoreduction in the first intervention is crucial for survival
Staging:

- FIGO:
  - Diagnosis: transvaginal sonography
  - Staging: intra operative
**STAGING:**

**DIAGNOSIS BY PREVIOUS SURGERY OR TISSUE BIOPSY (CYTOPATHOLOGY):**
- Obtain family history
- Refer for genetic risk evaluation
- Chest imaging
- CBC, chemistry profile with LFTs
- Institutional pathology review
- Ultrasound and/or abdominal/pelvic CT/MRI as clinically indicated
- CA-125 or other tumor markers as clinically indicated

**WORKUP:**
- Obtain family history
- Refer for genetic risk evaluation
- Abdominal/pelvic exam
- Chest imaging
- Complete blood count (CBC), chemistry profile with liver function test (LFT)
- GI evaluation as clinically indicated

- Ultrasound and/or abdominal/pelvic CT/MRI as clinically indicated
- CA-125 or other tumor markers as clinically indicated

**PRIMARY TREATMENT:**
- Laparotomy/total abdominal hysterectomy (TAH)/ bilateral salpingo-oophorectomy (BSO) with comprehensive staging or unilateral salpingo-oophorectomy (USO) (clinical stage 1A or 1C, all grades with comprehensive staging if patient desires fertility) or Cytoreductive surgery if clinical stage II, III, or IV or Consider neoadjuvant chemotherapy (category I)/primary interval cytoreduction (diagnosis by fine needle aspiration [FNA], biopsy, or paracentesis) for patients with bulky stage III/IV who are poor surgical candidates due to high-risk comorbidity conditions or disease factors

**PET/CT scan or MRI may be indicated for indeterminate lesions if results will alter management.**
Staging:

- PET/CT has no role in detection of ovarian cancer
  - Reported sens of 52–58% and spec of 76–78% for analysis of incidental adnexal lesions with PET-CT

- Most epithelial ovarian tumors have a high FDG avidity:
  - In advanced ovarian cancer FDG can provide information about extra abdominal disease
  - Peritoneal deposits < 1 cm can lead to false negatives

- For staging, the addition of FDG PET to contrast-enhanced CT improves accuracy

   MRI, CT, and PET/CT for ovarian cancer detection and adnexal lesion characterization.
   Diagnostic accuracy of integrated FDG-PET/contrast-enhanced CT in staging ovarian cancer: comparison with enhanced CT.
Stage ?:  

68 y.o. woman with ovarian carcinoma:  
Typical spread around the liver dome  
➢ Stage IIIC

PET/CT:  
Pathological FDG uptake in LN metastasis in the upper mediastinum  
➢ extra abdominal disease
Staging:

- Comparing ceCT with PET/ceCT:

  40 patients staged with ceCT and PET/ceCT, sensitivity and accuracy improved significantly with p values of $5.6 \times 10^{-7}$ and $1.2 \times 10^{-7}$, respectively. (Kitajima et al. EJNMMI 2008, 35:1912-20)
Follow up:

- Screening:
  - CA-125 (however NPV around 80%)
  - Elevated CA-125 or clinical Symptoms:
    - CE-CT or PET/CT?
    - FDG PET/CT has reported high PPV (89-98%) for recurrence and can give additional information about localisation for potential surgical treatment
    - Change in treatment of 44% (Mangili et al. J Nucl Med Mol Imag 2007)
    - Ce-CT and FDG PET-CT with similar accuracy for ovarian cancer recurrence, additionally SUV predictive for outcome (Sala et al. Recurrent Ovarian Cancer: Use of Contrast-enhanced CT and PET/CT to Accurately Localize Tumor Recurrence and to Predict Patients’ Survival, Radiology: 257, 125-134).
Pitfalls:

In unenhanced CT peritoneal carcinomatosis can mimic bowel loop activity

⇒ Contrast enhanced CT of the abdomen for ovarian cancer
Pitfalls:

Peritoneal carcinomatosis around the liver can mimic hepatic involvement:
⇒ This would over stage the patient form IIIC to IV

Ovarian cancer should be imaged with iv contrast.
Summary: Present and future of FDG-PET/CT in ovarian cancer

- For staging PET/CT with contrast (ce) is superior to ceCT and ceMR
  - Sens ca. 65% and spec ca. 78%
  - Limitation in assessing primary tumor extension in the pelvis, but superior in detection of LN and distant metastasis
- PET/CT can distinguish metabolic responder and non-responders
- Restaging: higher sens and spec than CT or MR
Germ cell tumors:

44 y.o. large lesion in the left adnex
- Teratoma

A mature teratoma is FDG negative.
FDG PET/CT in gynecology:

1. Physiological uptake
2. Ovarian cancer
3. Cervical carcinoma
4. Endometrial carcinoma
Introduction:

- 2nd most common cancer death in women worldwide (234’000 deaths per year)
- High discrepancy in mortality between developed (40’000 dpy) and developing countries (>190’000 dpy)
- In developed countries 71% of newly diagnosed cervical CA are stage I – IIA (screening)
Staging: FIGO + / -

The international Federation of Gynecology and Obstetrics: Only clinical staging system for cervical carcinoma
examination, colposcopy, biopsies of lesions, chest radiography, cystoscopy, sigmoidoscopy, excretory urography, barium enema

+ longstanding experience,
+ wide spread availability
- no N-staging!
- very limited evaluation of the tumor size
- Not accurate, compared with surgical staging:
  17-32 % errors in stage IB
  up to 67 % errors in stage II-IV

Staging:

NCCN Guidelines Version 1.2015
Cervical Cancer

- H&P
- Complete blood count (CBC) (including platelets)
- Cervical biopsy, pathologic review
- Cone biopsy as indicated
- Imaging (optional for ≤ stage IB1):
  - Chest x-ray
  - CT or PET-CT scan
  - MRI as indicated
- Smoking cessation and counseling intervention if indicated
- Consider HIV testing (category 3) Optional:
  - EUA cystoscopy/proctoscopy (≥ stage IB2)

Stage IA1 →
- Trachelectomy
- Hysterectomy

Stage IA2 →
- Trachelectomy & LN sampling
- Hysterectomy

Stage IB1 →
- Hysterectomy & LN resection

Stage IIA1 →

Stage IIB →
- Hysterectomy & LN resection

Stage IIA2 →

Stage IIB →

Stage IVA →

Chemoradiotherapie
### FIGO Therapy:

Waggoner SE, Lancet 2003; 361:2217-25:

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical Features</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>IA1</td>
<td>Invasion 3.0 mm or less</td>
<td>If patient desires fertility, conisation of cervix</td>
</tr>
<tr>
<td></td>
<td>With lymphovascular space invasion</td>
<td>If she does not, simple hysterectomy (abdominal or vaginal)</td>
</tr>
<tr>
<td>IA2</td>
<td>3.0–5.0 mm invasion, &lt;7.0 mm lateral spread</td>
<td>Hysterectomy with or without pelvic lymphadenectomy</td>
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<tr>
<td>IB1</td>
<td>Tumour 4 cm or less</td>
<td>Radical hysterectomy with pelvic lymphadenectomy</td>
</tr>
<tr>
<td>IB2</td>
<td>Tumour bigger than 4 cm</td>
<td>Radiotherapy</td>
</tr>
<tr>
<td>IIA</td>
<td>Upper-two-thirds vaginal involvement</td>
<td>Radical hysterectomy with pelvic lymphadenectomy plus chemoradiotherapy for poor prognostic surgical-pathological factors*</td>
</tr>
<tr>
<td>IIB</td>
<td>With parametrial extension</td>
<td>Chemoradiotherapy</td>
</tr>
<tr>
<td>IIIA</td>
<td>Lower-third vaginal involvement</td>
<td>Chemoradiotherapy</td>
</tr>
<tr>
<td>IVA</td>
<td>Local extension within pelvis</td>
<td>Chemoradiotherapy</td>
</tr>
<tr>
<td>IVB</td>
<td>Distant metastases</td>
<td>Chemoradiotherapy</td>
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**IIb or not IIb**
Nodal involvement: It has an impact!

In all FIGO stages N1 clearly decreases the survival. The extent of nodal involvement also has an impact on survival.
Staging today?

In the guidelines staging is still performed with clinical examination.

Although imaging: CT, MRI, PET or PET-CT is recommended for tumors stage > IB2

The additional information is added to the FIGO stage: eg. FIGO IIB-2, cN1, cM1
Local staging: Early stages

- MRI is superior to CT or PET/CT for the assessment of fertility preserving therapy:
  - For CIN – Stage IA => Cone Biopsy
  - FIGO stage IA1 with lymphovascular invasion, IA2, and IB1 => Trachelectomy

- Tumor < 2 cm
- 2 - 4 cm abdominal trachelectomy
- At least 1 cm from internal cervical os
- Infiltrating < ½ of cervical stroma thickness
Local staging:

- MRI is superior to CT or PET/CT for local extent and especially to delineate parametrial invasion
Lymph node staging:

- PET/CT is superior for lymph node metastasis:
  - For high risk cervical cancer: sensitivities 75-86% and specificities 92-97%
  - PET/CT detects lymph node metastases despite negative findings on CT/MRI

“PET/MRI identified all lesions depicted on PET/CT and significantly clarified the anatomic site of disease visualized on PET/CT.” Perry Grigsby, SNM 2013 (Washington University)
Cervical cancer:

- Combined pre-treatment MRI and \(^{18}\)F-FDG PET/CT parameters as prognostic biomarkers in patients with cervical cancer:

<table>
<thead>
<tr>
<th>DFS</th>
<th>HR</th>
<th>p</th>
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<tbody>
<tr>
<td>ADC</td>
<td>0.56</td>
<td>0.007*</td>
</tr>
<tr>
<td>PE</td>
<td>1.07</td>
<td>0.59</td>
</tr>
<tr>
<td>SUV(_\text{max})</td>
<td>1.12</td>
<td>0.18</td>
</tr>
<tr>
<td>TLG</td>
<td>1.03</td>
<td>0.024*</td>
</tr>
<tr>
<td>MTV</td>
<td>1.31</td>
<td>0.014*</td>
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Two patients both with FIGO IIA cervical cancer:

1) ADC 0.81 mm\(^2\)/s, SUV 11.1, MTV 18.4 ml, TLG 126 mg (DFS = 10 m; OS = 33.7 m)
2) ADC 0.97 mm\(^2\)/s, SUV 8.7, MTV 10.4 ml, TLG 53 mg (alive free of disease)

*Micco M, Vargas HA, Burger IA et al, Eur Radiol 2014 (Epub)*
Cervical cancer:

Lymph node metastasis inter aortocaval and iliacal
Conclusion staging:

MRI for local tumor extent:
- To evaluate for fertility sparing trachelectomy
- To detect parametrial invasion

PET/CT: according to ACR guidelines highly appropriate for nodal disease in Stage II or higher:
1. MRI seems to be inferior to PET in detecting lymph node metastasis
2. PET/CT is superior for distant metastasis

Potential future: PET/MR, PET/CT-Nomogram?
Nomogram for staging:

FDG-PET-based prognostic nomograms for locally advanced cervical cancer

PET Characteristics

1. Highest PET Lymph Node Level
   Pelvic
   None
   Aortic
   0 150 350 550

2. PET Tumor Volume
   0 5 15 25 35 45 55

3. Cervix Tumor SUV_{max}
   0 10 20 30 40 50 60 70 80 90 100

Points per Factor

Total Points

1-Year Recurrence-Free Survival
   0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1

3-Year Recurrence-Free Survival
   0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1

Concordance index and SD

<table>
<thead>
<tr>
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<th>Training</th>
<th>Testing</th>
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<tbody>
<tr>
<td>A. PET-based nomograms</td>
<td>0.740 ± 0.011</td>
<td>0.741 ± 0.099</td>
</tr>
<tr>
<td>Recurrence-free survival</td>
<td></td>
<td></td>
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<tr>
<td>Disease-specific survival</td>
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Restaging:

1. Therapy response assessment
2. Detection of recurrence
Therapy response assessment:

KM curves for Survival based on post therapy FDG PET in 378 patients: 269 complete, 52 persistent abnormal FDG uptake, 57 new sites of disease.

Recurrence detection:

- No reliable serum marker
- Cytological evaluation limited after radiotherapy
  - Recurrence often only detected when clinical manifestation

40 yo adenocarcinoma of the cervix, treated with RCTx (03/11) initial CR
02/12 local recurrence in the anterior wall of the uterus (arrow) and in iliacal
as well as mesenterial LN (arrow head).
Recurrence management:

- If recurrence confined to the pelvis best therapy option: **Pelvic exenteration**
  - PET/CT to rule out distant metastasis
  - MRI for local extent: for surgery planning organ or side wall invasion is critical
Recurrence management:

- MRI-PET superior?
Restaging cervical cancer:

Supraclavicular lymph node metastasis
Restaging cervical cancer:
Cervical cancer: complications

Silent right kidney due to obstruction
Restaging recurrence?:

43 y.o. cervical Ca FIGO IIa
After surgery and radiation
- Two retroperitoneal cystic lesions with mild FDG uptake
- Recurrence?

- Ovariopexy
Conclusion restaging:

**Therapy response assessment:**
- PET/CT is superior to CT or MRI to predict response
- Complete metabolic response is the best predictor for a favorable outcome

**Recurrence management:**
- No reliable blood or PAP smear screening
- PET/CT is superior to CT or MRI to predict extra pelvic disease
- MRI is superior to PET/CT for local extent
- PET/MRI high potential for this demanding situation
FDG PET/CT in gynecology:

1. Physiological uptake
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Endometrial carcinoma:

Epidemiology:
Age: 55-65 y.o.
Incidence: 0.04%
Mortality: 2-5/100’000

Most present with an early stage:
postmenopausal or irregular bleeding
5 J-DFS: 80-90%

Advanced disease has high risk for relapse
Endometrial carcinoma:

Staging:
IA  Tumor confined to the uterus, < ½ myometrium invasion
IB  Tumor confined to the uterus, > ½ myometrium invasion

II  Cervical stromal invasion

IIIA Tumor invades serosa or adnexa
IIIB Tumor invades vagina
IIIC Pelvic or para-aortic lymph node involvement

IVA Bladder/bowel invasion
IVB Distant metastasis, inguinal lymph nodes
Staging:

Transvaginal sonography

Surgery with lymphadenectomy for staging (Stadium IB or more, IA G1 & G2 no lymphadenectomy)

If further imaging: MRI
- Invasion of the myometrium?
- Invasion of the cervix?
- Invasion of adjacent organs?
Staging:

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Endometrial Carcinoma

INITIAL CLINICAL FINDINGS

ADDITIONAL WORKUP

Suspected extraterine disease (endometrioid histology)\(^a\)
• CA-125 (optional)
• MRI/CT/PET, as clinically indicated

None

Intra-abdominal:
• Ascites
• Omentum
• Nodal
• Ovarian
• Peritoneal

Initially unresectable extraterine pelvic disease:
• Vaginal
• Bladder
• Bowel/rectum
• Parametrial

Extra-abdominal/liver
Role of the integrated FDG PET/CT in the surgical management of patients with high risk clinical early stage endometrial cancer: Detection of pelvic nodal metastases

FDG-PET/CT can detect pelvic lymph node metastasis: Sens 77.8%, spec 100%, PPV 100% and NPV 93.1%

FDG-PET/CT could be used to stage patients with high risk endometrial cancer to select patients that benefit from radical lymphadenectomy.
Role of [18F]FDG PET/CT in endometrial cancer staging
Detection of Lymphnodemmetastasis: Sens / Spec: 57 / 100%
Detection of distant metastasis: Sens / Spec: 100 / 96%
Restaging:

65 y.o. Endometrial Ca FIGO IIIC
After surgery and radiation

- Iliacal lymph node metastasis with high FDG activity
Uterine leiomyomas: Overview of different leiomyomas (Kitajima et al):

- No uptake (SUV 2.0)
- Moderate uptake (SUV 3.9)
- High uptake (SUV 8.5)
Thank you!