RECIST 1.1 still appropro?
What are the alternatives?
And, Imaging in Cervix Cancer

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J Robert and Ann K Stewart Endowed Professorship

Gynecologic Cancer InterGroup
Imaging & Pathology Brainstorming Day
Munich, October 17, 2018
I have funding from Elekta for a clinical trial

Recipient of a U10 LAPS grant to HCI

Co-Chair Gyn Cancer Steering Committee
What % of clinical trials are not successful?
Why?

FDA estimates 92% of trials are not successful, and of 95% of oncology trials ~1/2 fail due to other reason than efficacy.
Adult Cancer Clinical Trials That Fail to Complete: An Epidemic?


Figure 1. Reasons for adult cancer clinical trials failing to complete. Breakdown of the reasons for failure to complete among 935 adult interventional cancer clinical trials.
Clinicaltrials.gov

7776 Phase II-III trials

2005-2011

20% failure at 7 yrs.

48,000 patients enrolled in trials that failed to complete
When should you involve the statistician?
(a) Never
(b) 18 hours before the SGO/ASCO abstract deadline
(c) When you have an Excel spreadsheet w/ some data
When should you involve the statistician?

- (a) Never
- (b) 18 hours before the SGO/ASCO abstract deadline
- (c) When you have an Excel spreadsheet w/ some data
- (d) From the beginning of trial idea thru publication!!
The science of response? Or, which RECIST?

- **WHO 1981**
  - Bidirectional measurements
  - >50% tumor shrinkage for PR
  - >25% tumor increase for progressive disease

- **RECIST 2000**
  - Unidimensional measurement
  - >30% tumor shrinkage for PR
  - > 20% tumor increase for progressive disease

- **RECIST 1.1 2009**
  - # of lesions reduce from max. of 10 to 5
  - Short axis of LNs >15mm are assessable
  - 5 mm absolute increase is required to prevent overcalling Progressive Disease
The science of response?

- Immune-Related Response Criteria (irRC) 2009
  - RECIST did not take into account delay between dosing and response
  - New lesions are a change in tumor burden, and not independently lead to PD
  - Retained bidirectional measurements by WHO
  - Important in development of ipilimumab and tremelimumab
  - irCR: disappearance of all lesions
  - irPD: >25% tumor increase in tumor burden
  - IrSD: everything else

- PET Response Criteria in Solid Tumors (PERCIST) 2009
  - Complete Metabolic Response (CMR): lesion < mean liver activity and at level of blood pool activity
  - Partial Metabolic Response (PMR): >30% decrease in SUV, and no new lesions
  - Progressive Metabolic Disease (PMD): >30% increase in SUV, or new lesions
Not everyone loves Recist 1.1

Advances in oncological treatment: limitations of RECIST 1.1 criteria
Grimaldi S, et al. 2018

- **Recist 1.1**
  - Reduced # of target lesions (max 5, 2 per organ)
  - Revised assessment of lymph nodes
  - Clarified the role of other imaging modalities
  - Designed to evaluate tumor response to cytotoxic therapies (mostly phase II trials)

- **Limitations of Recist 1.1**
  - Some lesions are difficult to assess with dimensional criteria
    - Complex shapes, leptomeningeal disease, pleural or pericardial effusions, ascites, inflammatory breast cancer, lymphangitic spread
  - SBRT/RT may take months to decrease in size
  - **Targeted therapies** may have prolonged minimal regressions in tumor size or durable disease stability: late and durable responses may occur
Future directions for response assessment

Advances in oncological treatment: limitations of RECIST 1.1 criteria
Grimaldi S, et al. 2018

- Attention should be given to assessment tools going beyond tumor size or tumor burden

- Strategies include: volumetric imaging, kinetic models, dynamic contrast-enhancement techniques, radiomics, functional imaging and multi-parametric approaches

- CT
  - DCE: kinetics of contrast uptake (eg antiangiogenics)

- MRI
  - DWI (Diffusion Weighted Imaging)
  - ADC (Apparent Diffusion Coefficient)
    - Provides info about edema, fibrosis, necrosis and apoptosis
  - CE-MRI (Contrast Enhanced-MRI)
    - Evaluates blood supply and treatment-induced necrosis

- PET
  - FDG PET is standard in Lymphomas and other tumor types
  - New tracers can measure: Receptors, cell trafficking, DNA synthesis, membrane renewal, perfusion, hypoxia, etc...

- Radiomics
  - extraction of quantitative data from regions of interest on either pre- or post-treatment images
  - Statistics from the intensity histogram of the region of interest, relationships with neighbouring voxels, sphericity, roughness or spiculation are assessed
More about response assessment

Who does the radiologic measuring?

- ~20 different forms of RECIST
- Trial specific measurements
- Labor intensive
- Research task—not billable clinical service
- Beware of protocol with multiple different imaging measurements
- Proprietary products
- Do you have a radiologist on your PRMC?
Center For Quantitative Cancer Imaging:

Tumor Imaging Response Assessment

- Collaboration with Dana-Farber/Harvard Cancer Center using PIM Software
- CQCI provides image measurements and response assessment in HCI trials

Dedicated Image Analysis Software

Web-based Database
CQCI-Supported Imaging Response Criteria

- Imaging Response Assessment ≠ RECIST

- Currently supported imaging response criteria (>25)
  - Solid Tumors: WHO, mWHO, RECIST, RECIST 1.1, Choi, mRECIST, irRC, irRECIST, iRECIST
  - Neuro: Macdonald, RANO, iRANO
  - Lymphoma: Cheson, Modified Cheson, Deauville, Lugano, LYRIC
  - Myelofibrosis: IWG-MRT
  - Chronic Lymphocytic Leukemia: IWCLL

- Multiple Myeloma: IMWG, International Uniform Response Criteria Consensus Recommendations
- Prostate: PCWG2, PCWG3
- FDG-PET: EORTC, PERCIST

- Frequent protocol-specific modifications by PI/Sponsor

- Many trials use multiple criteria (e.g., RECIST 1.1. + irRECIST)
Can Biomarkers be used as a Primary Endpoint?
Integral versus Integrated Marker?

Development and Use of Integral Assays in Clinical Trials

Schilsky et al, Clin Cancer Res 18:1540-6, 2012

Box 1. Characteristics of integral markers

- Integral markers are required for the trial to proceed and are used for medical decision making.

- Integral markers are used
  - to determine patient eligibility (e.g., somatic mutation for a kinase inhibitor)
  - to assign patients to treatment [e.g., FLT3-ITD for risk assessment in pediatric trials with consequent assignment to specific treatment (17)]
  - for risk stratification if such stratification leads to different treatments (as in the FLT3-ITD example)
  - for risk classification (as in the FLT3-ITD example)

- Because the assay is performed for medical decision making, and the patient or physician is informed of the result, a Clinical Laboratory Improvement Amendments–certified laboratory is generally required for assay.

- Integrated markers are performed on all or a statistical subset of patients, but are not used for medical decision making.

- Research markers include all other assays; often referred to as correlative research.
Ongoing Trials – status update

PORTEC-4a

Randomisation

Individual treatment recommendation based on molecular pathology analysis

- Favourable
  - Observation (~55%)
- Intermediate
  - Vaginal brachytherapy (~40%)
- Unfavourable
  - External beam radiation therapy (~5%)

Standard treatment recommendation based on clinicopathological factors

- Vaginal brachytherapy

Follow-up and Quality of Life
Endpoints in clinical trials

Where are the opportunities?

- Neoadjuvant therapy in ovarian cancer
  - Tissue, pathways, etc..
- Cervix
  - Functional endpoints
- Window trials
  - NRG GY011
Chemotherapy Response Score: Development and Validation of a System to Quantify Histopathologic Response to Neoadjuvant Chemotherapy in Tubo-Ovarian High-Grade Serous Carcinoma

Bohm et al JCO 2015

- Three-Tier CRS System Shows Prognostic Significance and High Reproducibility
- Test and Validation Set were both significant
- CA-125 Response to NACT Is Not Predictive of CRS
- CRS Adds Prognostic Information to Debulking Status
- CRS 3 Identifies Patients With Low Probability of Primary Platinum-Resistant Disease
Functional Imaging Endpoints:
NRG Radiation Therapy and Cisplatin With or Without Triapine in Treating Patients With Newly Diagnosed Stage IB2, II, or IIIB-IVA Cervical Cancer or Stage II-IVA Vaginal Cancer

- Primary endpoint: PFS
- Secondary endpoint: PET response
• **Primary Endpoint/Objective**
  • PFS

• **Secondary Objectives**
  • Determine PET/CT response by treatment arm
  • OS
  • GI adverse events for IMRT vs 3DRT
  • Acute adverse events (CTCAE v4.0)
  • Chronic adverse events (CTCAE v4.0)

• **Tertiary Objectives**
  • Methemoglobin pre and post Triapine
  • Does knowledge based planning with NCTP modeling improve IMRT plans

1. Beware of a “plethora” of endpoints---require clinicaltrials.gov reporting
2. Adhere to the KISS philosophy
NRG-GY011
(ClinicalTrials.gov NCT #TBD)

A Randomized Surgical Window Pilot Investigation of the Relationship of Short Term Medroxyprogesterone Acetate (NSC #26386) Compared to Medroxyprogesterone Acetate Plus Entinostat (NSC #706995) on the Morphologic, Biochemical, and Molecular Changes in Primary Endometrioid Adenocarcinoma of the Uterine Corpus

NCI Version Date: 08-01-17

- **Primary Endpoint/Objective**
  - Progesterone receptor score measured between the two arms

- **Secondary Objectives**
  - Histologic tumor response between the two arms
  - Ki67 score between the two arms
  - Adverse events (CTCAE v4.0)

- **Exploratory Objectives**
  - Estrogen receptor score measured between the two arms
  - p21 receptor score measured between the two arms
  - Co-Expression of PR, K67 and p21 receptor score measured between the two arms

N=40
Opened 8/2/16
Closed 2/9/17
Improvement in QOL may be more relevant to the patient with an advanced recurrent cancer than response or PFS.

Women with ovarian cancer would be willing to sacrifice 5 months of PFS for a reduction in treatment-related toxicity—from severe neuropathy to mild neuropathy.

Use of targeted therapies might allow small randomised trials in very select populations with an anticipated large difference in outcome.
What are the endpoints for clinical trials in Recurrent Ovarian Cancer?

- OS is the preferred endpoint for patient cohorts with an expected median OS ≤ 12 months.
- “PFS is an alternative, and it is the preferred endpoint when the expected median OS > 12 months. However, PFS alone should not be the only endpoint and must be supported by additional endpoints including pre-defined patient reported outcomes (PROs), time to second subsequent therapy (TSST), or time until definitive deterioration of quality of life (TUDD).”

Composite Endpoints for Clinical trials

- Integrates tumor response rates, survival, toxicity, and PROs into a single metric and may better capture therapeutic benefit
- Possible important indicator of response and predictor of survival
- **Clinical Benefit Response**: Assessment of pain, performance status and weight
- **Overall Treatment Utility**: Clinical and radiologic response, toxicity, adverse events and patient-reported acceptability of treatment
- **QAPFS**: Quality Adjusted PFS
- **TWiST**: Time without symptoms of disease or toxicity
PROs as Endpoints

Or, Clinical relevance is not restricted to survival!
Patient Reported Outcomes

- “a measure of the patient’s health condition that comes directly from the patient or caregiver without interpretation of the response by a medical provider”
- Likely follow the course of a patient’s disease, side effects, and function in a more clinically meaningful way than traditional outcome criteria
- An average patient should be able to complete a PRO instrument within 10-15 min
- Implementation can be facilitated with the EMR

Moss and Havrilesky, Gyn Oncol 148:12-18, 2018
FDA: surrogate endpoints such as PFS supported by PROs will be used for accelerated approval.

Recent examples:
- Bevacizumab in platinum-resistant recurrent ovarian cancer (Aurelia data, improved PFS with >15% improvement in abdominal symptoms)
- Olaparib in the maintenance setting (SOLO2 data, improved PFS without symptoms of disease or toxicities)

Moss and Havrilesky, Gyn Oncol 148:12-18, 2018
PROs: Incorporated in Cost Effectiveness

- Cost-utility analyses measure effectiveness in terms of QALYs: time in years multiplied by a utility weight specific to condition or treatment
- PROs (eg EQ-5D) can generate a utility weight
- For value based payments
  - Bonus payments may be available if PROs are being captured by the EMR

Moss and Havrilesky, Gyn Oncol 148:12-18, 2018
PROs: Gyn Clinical Research

- Many outstanding examples in advanced stage trials, but....
  - In a systemic analysis of 50 randomized gyn trials only 1/3 informed clinical decision making
  - In a review of 26 ovarian cancer randomized trials only 1/3 included a PRO objective

- Plethora of instruments
  - FACT is recommended for social implications or long term effects
  - QLQ may be preferred for assessing physical functioning

Moss and Havrilesky, Gyn Oncol 148:12-18, 2018
Patient-Reported Toxicity During Pelvic Intensity-Modulated Radiation Therapy: NRG Oncology–RTOG 1203

JCO 2018

Ann H. Klopp MD, PhD
MD Anderson Cancer Center


This project was supported by grants U10CA180868 (NRG Oncology Operations), U10CA180822 (NRG Oncology SDMC), UG1CA189867 (NCORP) from the National Cancer Institute (NCI)
Concave target allows IMRT to reduce dose to small bowel in center of pelvis.

Retrospective studies show lower rates of acute and chronic GI toxicity.

Prospective, non-randomized study (RTOG 0418) found IMRT to be feasible in a multi-center study, and result in favorable rate of acute 2+ GI toxicity (25%)
Objectives

**Primary**
Determine if acute GI toxicity is reduced with IMRT in week 5 of RT using patient reported measure of toxicity (EPIC Bowel)

**Secondary**
- Acute urinary toxicity (EPIC tool)
- Quality of life (FACT)
- LRC, DFS, OS
- Validate EPIC in women
- Health utilities analysis

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before RT</td>
<td>Baseline</td>
</tr>
<tr>
<td>3 weeks after RT start</td>
<td>Compare early acute toxicity</td>
</tr>
<tr>
<td>End of RT (5 weeks after RT start)</td>
<td>Maximum difference in acute toxicity</td>
</tr>
<tr>
<td>4-6 weeks after RT</td>
<td>Compare resolution of acute toxicity</td>
</tr>
<tr>
<td>1 year from the start of RT</td>
<td>Early chronic toxicity</td>
</tr>
<tr>
<td>3 years from the start of RT</td>
<td>Long term toxicity</td>
</tr>
</tbody>
</table>
Eligibility

Women with endometrial or cervical cancer requiring post-op pelvic RT or chemoRT

Stratification Factors

**XRT Dose:** 45 Gy, 50.4 Gy

**Chemo:** No chemo, 5 cycles of weekly cisplatin at 40mg/m²

**Disease Site:** Endometrial, Cervix

**RANDOMIZE**

IMRT pelvic radiation treatment

4-field pelvic radiation treatment
A

Change in EPIC Bowel Score

Week 3 of RT
IMRT 110
Four-field RT 127
Week 5 of RT
IMRT 107
Four-field RT 126
4 to 6 weeks post-RT
IMRT 99
Four-field RT 121

B

Change in EPIC Urinary Score

Week 3 of RT
IMRT 110
Four-field RT 127
Week 5 of RT
IMRT 107
Four-field RT 126
4 to 6 weeks post-RT
IMRT 99
Four-field RT 121

* indicates statistically significant difference.
Fig 3. Patient-Reported Outcomes—Common Terminology Criteria for Adverse Events scores after 5 weeks of radiation treatment. High toxicity scores were considered as selection of level 4 or 5 responses with each question on a 5-point scale. These level 5 and 5 responses for each question were the following: [1] frequently or almost constantly; [2] quite a bit or very much; [3] severe or very severe. (*) Statistically significant difference. IMRT, intensity-modulated radiation therapy; RT, radiation therapy.
Conclusions

- Pelvic IMRT reduces acute patient reported GI and GU toxicity compared to standard pelvic RT.
- Pelvic IMRT reduces need for anti-diarrheal medications as compared to standard pelvic RT.
- Pelvic IMRT improves quality of life during treatment as compared to standard pelvic RT.
- Longer term follow up will determine if these differences in acute toxicity result in lower rates of late toxicity.
Pre-treatment vs. Post-treatment: HR-CTV 100%
Is Imaging Imperative in Cancer of the Cervix?

1. Historic Good Results
2. Imaging Renaissance

Stockholm

Paris

Manchester

<table>
<thead>
<tr>
<th>Stage</th>
<th>% 5 yr cure (RT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>79</td>
</tr>
<tr>
<td>II</td>
<td>41</td>
</tr>
<tr>
<td>III</td>
<td>27</td>
</tr>
</tbody>
</table>

Regaud, Paris: 1922-26, n=329
FIGO: Clinical Staging system!

- IA1 ≤ 3 mm invasion, IA2 3-5 mm invasion (< 7 mm horizontal spread)
- IB1 ≤ 4 cm, IB2 > 4 cm
- IIA1 ≤ 4 cm, IIA2 > 4 cm* FIGO 2009 change.

ICRU 89
Staging and Imaging in Cervix Cancer

- FIGO permits:
  - EUA, colposcopy, endocervical curettage, hysteroscopy,
  - Cystoscopy, proctoscopy, IVP, chest Xray, skeletal Xrays

- Imaging (my preference)
  - PET/CT pretreatment for nodal evaluation and to evaluate response 3 months post treatment
  - MRI for evaluation of local tumor extent (eg brachy planning)
  - MRI at first brachy insertion (Image guided brachy)
MRI vs CT vs PET in cervix cancer staging?


41 studies with histologic confirmation

PET or PET/CT had an overall higher diagnostic performance than did CT or MRI in detecting metastatic lymph nodes in patients with cervical cancer.
Sentinel node biopsy has greater accuracy in determining lymph node status among women with primary cervical cancer than current commonly used imaging methods.

- 72 studies
- 5042 women
PET in Cervix Cancer: Is it any good?

- Staging?
- Predictive of outcome?
- Asymptomatic recurrences?
- Can PET + LN’s be cured with standard doses?
Fig 2. Kaplan-Meier (A) recurrence-free survival for all 513 patients

A. Recurrence-Free Survival (probability)

B. Disease-Specific Survival (probability)

C. Disease-Specific Survival (probability)

D. Disease-Specific Survival (probability)

E. Disease-Specific Survival (probability)

Stage I

Stage II

Stage III

> 35% DSS
Post treatment PET can be highly predictive

The Role of $^{18}$F-FDG PET in Assessing Therapy Response in Cancer of the Cervix and Ovaries


![Graph showing cumulative survival for different response categories with n=269 for complete response, n=52 for partial response, and n=57 for progressive disease.](image)

**Table 2.** Results of Final Multivariate Proportional Hazards Model for Survival Outcome

<table>
<thead>
<tr>
<th></th>
<th>Posttherapy PET</th>
<th>Lymph Node Status by Pretreatment PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coefficient</td>
<td>Progressive</td>
<td>Persistent</td>
</tr>
<tr>
<td></td>
<td>Disease</td>
<td>Disease</td>
</tr>
<tr>
<td>SE</td>
<td>3.48</td>
<td>1.84</td>
</tr>
<tr>
<td>Coefficient/SE</td>
<td>0.59</td>
<td>0.43</td>
</tr>
<tr>
<td>$\chi^2$</td>
<td>5.89</td>
<td>4.31</td>
</tr>
<tr>
<td></td>
<td>34.69</td>
<td>18.56</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>32.57 (10.22-103.82)</td>
<td>6.30 (2.73-14.56)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Abbreviations: CI, confidence interval; PET, positron emission tomography; SE, standard error.*
12% (9/78) of patients had an asymptomatic recurrence with a median time to recurrence of 16 months.
Eligibility: IB2, IIA2, IIB- IVA

153 patients had PET and CT and Pathology

43 patients had positive lymph nodes
“Conclusion: Addition of PET to DCT resulted in statistically borderline increase in sensitivity to detect LN metastasis in abdomen in advanced cervical cancer.”

*Modern CT is very good.*
INTRAOPERATIVE ULTRASOUND

- CT-based study showed a perforation rate of 14% (experienced investigators)
  - Still occurred 8% when physician was confident of correct placement
  - Physician concern, age > 60, and tumor size were predictors of perforation

- US should be used to avoid perforation
  - If perforation: consider antibiotics

- US can be used for treatment planning and IGBT

Barnes et al IJGC 17(4):821-6, 2007
ICRU Reports

Internationally acceptable recommendations regarding:

• Quantities and units of ionizing radiation and radioactivity
• Procedures suitable for the measurement and application of these quantities
• Physical data needed in the application of these procedures

• ICRU 38 was published in 1985
• Formalization of GEC-ESTRO guidelines
• Describes prescribing, recording, and reporting cervix cancer brachytherapy
• Beautifully written, 258 pages
ICRU 89 Principle

1. Use imaging to conform the dose to the target
2. Effectively spares OARs
The initial evaluation begins with clinical gynecologic examination and documentation and by drawing of the findings on clinical diagrams.

Initial staging involves MRI, CT, or PET-CT, where available... The use of US, radiography (chest, IVP, skeletal), and scintigraphy can also be helpful, but the information they provide is more limited.

Monitoring of disease regression during radiation treatment is important and is done through the use of repeated gynecologic examinations and imaging studies, before and at the time of brachytherapy to document disease regression and to plan brachytherapy.
Conclusions

- Think beyond PFS and OS as endpoints
- FIGO should consider abridging the staging system to permit cross sectional imaging
- Thanks for your attention