### Aims of Workshop
This course will outline the epidemiology of cervical and endometrial cancer throughout the world. Treatment options will be discussed with an emphasis on pelvic radiotherapy and the latest trends to minimize treatment related side effects. Representative patient case presentations will be used to highlight the urologic, gynecologic and physiotherapy management options for acute and late complications of radiotherapy on the bladder, lower urinary tract, vagina and pelvic floor.

### Learning Objectives
1) What are the potential urinary side effects from pelvic radiation and brachytherapy and how can this toxicity be decreased or minimized for cervical and endometrial cancer patients requiring radiation therapy as part of their treatment?
2) What are the latest trends for managing the acute and late complications of radiotherapy on the bladder, lower urinary tract and pelvic floor?
3) Where should future research efforts be directed to minimize and treat the long term unintended side effects of pelvic radiotherapy in women?

### Learning Outcomes
After the course, the participant will be able to:
1) Discuss different radiation treatment approaches for cervical and endometrial cancer and potential acute and long-term urinary side effects of pelvic radiotherapy and brachytherapy.
2) Describe the management of radiation induced bladder dysfunction following pelvic radiotherapy.
3) Outline the latest treatment options and considerations for radiation induced vulvar and pelvic floor dysfunction.

### Target Audience
Providers (MD, NP, PA, RN) who evaluate and care for women with lower urinary tract symptoms, hematuria, prolapse or pelvic floor dysfunction following pelvic radiotherapy.

### Advanced/Basic
Basic

### Conditions for Learning
This course will be interactive with specific case examples presented throughout the workshop session and a question-answer session after each speakers presentation.

### Suggested Learning before Workshop Attendance
Workshop attendees will be provided with suggested reading which will complement the lectures, case presentations and discussion.

### Suggested Reading
Elizabeth Kidd
- Dr. Kidd will provide background for the types of radiation treatment used for managing endometrial and cervical cancers, and representative cases will be discussed to help demonstrate specific genitourinary toxicity commonly experienced by patients. Relevant endometrial and cervical cancer epidemiology will also be covered along with existing data on the time course for bladder toxicity.
- Additionally, recent studies related to treatment advances for gynecologic cancers that help decrease urinary toxicity will be discussed, including: 1) the use of brachytherapy instead of external beam radiation for early stage high-risk endometrial cancer patients, 2) the use of intensity modulated radiation therapy (IMRT) to decrease dose to the bladder compared to standard pelvic external beam radiation therapy, and 3) the use of image-guided brachytherapy for intact cervical cancer for better defining the target volumes, organs at risk and normal tissue dose constraints.

Take home message: Treatment of endometrial and cervical cancers often requires radiation, which can cause genitourinary toxicity. Gynecologic cancer patients can live many years after their treatment, making long-term urinary tract toxicity a particular concern. Recent advances in treatment can help decrease the dose to the bladder and urinary tract.

Amy Dobberfuhl
- Dr. Dobberfuhl will review the pathophysiology of the early, latent and chronic phases of radiation induced bladder dysfunction. A systematic approach to the evaluation of radiation induced lower urinary tract complications in the female will be outlined, with an emphasis on: stress urinary incontinence, detrusor overactivity, mixed urinary incontinence, loss of bladder compliance, urothelial hemorrhage, fistula and erosion.
- Dr. Dobberfuhl will present an evidence based review of the most appropriate management strategies for both 1) acute genitourinary radio-toxicity during the early-phase after radiotherapy and 2) late-phase bladder and lower urinary tract complications.

Take home message: Management of the acute and long term adverse effects of radiation induced bladder dysfunction can be complicated and frustrating. Since chronic radiation damage is generally irreversible, the available treatment options are primarily palliative and should be focused on symptom management.

Bertha Chen
- Dr. Chen will review the clinical presentation and evaluation of radiation induced pelvic floor and vaginal dysfunction in women. Her discussion will include data on the impact on quality of life and treatment options for dyspareunia, pelvic pain, pelvic floor dysfunction and vaginal stenosis.
- Since urinary incontinence and pelvic organ prolapse is prevalent in women, a significant portion of female cancer patients may require management of these conditions before and after radiation. Dr. Chen will review the potential negative effects of radiation therapy on pelvic organ prolapse and discuss management options.
- Dr. Chen will provide a brief overview of the current areas of research in radiation induced bladder and pelvic floor dysfunction, and discuss areas of translational research.

Take home message: Radiation induced pelvic floor dysfunction is common. Awareness, early identification of the problem by the medical team, and early institution of treatment can help increase cancer survival wellbeing.

Stephanie Bernard
- Stephanie Bernard will review the different known effects of radiotherapy on the anatomical structure and biological function of the pelvic floor muscles, and how these muscular dysfunctions can contribute to urinary incontinence. There will also be an in depth discussion of the most common and readily available tools for clinicians to assess and diagnose pelvic floor muscle dysfunction.
- Additionally, Stephanie Bernard will outline the physiotherapy management of pelvic floor dysfunction related to urinary incontinence in gynecologic cancer survivors. A systematic approach will be applied using recent published evidence, ongoing research and representative cases to illustrate and support each treatment strategy.

Take home message: Radiotherapy for the treatment of gynecologic cancer leads to various pelvic floor muscle dysfunctions, which can further impair the continence mechanism. Although radiation damage is permanent, pelvic floor muscle function can be trained and optimized, leading to improved urinary continence and quality of life.
W9: Radiotherapy of cervical and endometrial cancer – Prevention and management of lower urinary tract, vaginal, vulvar and pelvic floor dysfunction in cancer survivors

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AMY D. DOBBERFUHL, M.D.¹ (UROLOGY)  
BERTHA CHEN, M.D.¹ (OBSTETRICS & GYNECOLOGY)  
STEPHANIE BERNARD, Ph.D.(C) P.T.² (PHYSIOTHERAPY)

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²UNIVERSITÉ LAVAL, QUÉBEC CITY, QUÉBEC, CANADA

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Tuesday, August 28th, 2018

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Bertha Chen (CIRM DISC1-08731, TRAN1-10958)
Stephanie Bernard (Université Laval, CIRRIS)

*All financial ties (over the last year) that you may have with any business organisation with respect to the subjects mentioned during your presentation.

Funding for speaker to attend:

☐ Self-funded  
☒ Institution (non-industry) funded  
☐ Sponsored by: N/A

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Step 2, locate workshop
Step 3, scroll to find evaluation button
Step 4, complete survey – enter email at end to enter prize drawer

• A shortened version of the handout has been provided on entrance to the hall
• A full handout for all workshops is available via the ICS website.
• Please silence all mobile phones
• PDF versions of the slides (where approved) will be made available after the meeting via the ICS website so please keep taking photos and video to a minimum.

OVERVIEW
Aims of Workshop

1. Outline the epidemiology of cervical and endometrial cancer throughout the world.

2. Review pelvic radiotherapy treatment options and the latest trends to minimize treatment related side effects.

3. Highlight the urologic, gynecologic and physiotherapy management options for acute and late complications of radiotherapy on the bladder, lower urinary tract, vagina and pelvic floor.

Learning Objectives

1. What are the potential urinary side effects from pelvic radiation and brachytherapy and how can this toxicity be decreased or minimized for cervical and endometrial cancer patients requiring radiation therapy as part of their treatment?

2. What are the latest trends for managing the acute and late complications of radiotherapy on the bladder, lower urinary tract and pelvic floor?

3. Where should future research efforts be directed to minimize and treat the long term unintended side effects of pelvic radiotherapy in women?

Outline

<table>
<thead>
<tr>
<th>Time</th>
<th>Speaker(s)</th>
<th>Topic</th>
</tr>
</thead>
<tbody>
<tr>
<td>11:00</td>
<td>Elizabeth Kidd</td>
<td>Minimizing radiation toxicity to benign tissues (Radiation Oncologist)</td>
</tr>
<tr>
<td>11:20</td>
<td>Amy Dobberfuhl</td>
<td>Acute and chronic lower urinary tract dysfunction (Urologist)</td>
</tr>
<tr>
<td>11:40</td>
<td>Bertha Chen</td>
<td>Radiation induced vaginal dysfunction (Urogynecologist)</td>
</tr>
<tr>
<td>12:05</td>
<td>Stephanie Bernard</td>
<td>Physiotherapy of the radiated pelvic floor (Pelvic Floor Physiotherapist)</td>
</tr>
<tr>
<td>12:25</td>
<td>Discussion</td>
<td>Bertha Chen</td>
</tr>
</tbody>
</table>
Example case (continued)

- December 2016 (age 45) – No evidence of disease but complaints of urinary leakage
- Feb. 2017 – Seen by urology
  - Diagnosed with mixed urinary urge and stress incontinence, daytime urgency and frequency, and nocturia
- March 2017 – Normal cystoscopy, urodynamics study showed detrusor overactivity
  - Treated with Detrol 2mg with little improvement
  - Treated with Vesicare 10 mg with some improvement

Cervical Cancer Background

Endometrial Cancer Background

- Types of radiation given
  - Early stage – surgery alone or surgery + vaginal brachytherapy
  - More advanced stage – pelvic radiation +/- vaginal brachytherapy

Endometrial Cancer – Types of radiation given

- Early stage – surgery alone or surgery + post-operative pelvic radiation
- More advanced stage – pelvic radiation + tandem & ovoid brachytherapy

Cervical Cancer – Types of radiation given

- Early stage – surgery alone or surgery + post-operative pelvic radiation
- More advanced stage – pelvic radiation + tandem & ovoid brachytherapy

Urinary Toxicity from Radiation
Region of Bladder Irradiated and Urinary Toxicity

- On multivariate analysis of 243 prostate cancer patients receiving radiation:
  - Urinary incontinence associated with mean trigone dose
  - Hematuria associated with bladder wall dose (V75) and cardiovascular disease
  - Pain during urinating associated with trigone dose (V75) and TURP

Schaake W et al. PLOS One 2018

LUTS in cervical cancer survivors after concurrent chemoradiation vs. rad hys

- 70 cervical ca survivors at least 3 yr out from treatment w/concurrent cheemoRT (EBRT + Brachy) vs. type III Rad Hys (no pre or post-op RT)
- More advance stage in CRT

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CRT (N=35)</th>
<th>RH (N=35)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years) + SD (range)</td>
<td>55.1+9.4 (42-77)</td>
<td>51.6+8.2 (38-49)</td>
<td>0.10</td>
</tr>
<tr>
<td>Mean age at treatment (years) + SD (range)</td>
<td>40.9+9.3 (26-72)</td>
<td>46.3+7.6 (28-59)</td>
<td>0.18</td>
</tr>
<tr>
<td>Mean post-treatment interval (years) + SD (range)</td>
<td>3.8+2.8 (3-13)</td>
<td>5.7+2.5 (3-14)</td>
<td>0.44</td>
</tr>
<tr>
<td>Median parity (stage)</td>
<td>2 (0-10)</td>
<td>2 (0-6)</td>
<td></td>
</tr>
</tbody>
</table>


Similar rates of lower urinary tract symptoms but different predominant symptoms

<table>
<thead>
<tr>
<th>LUT symptoms</th>
<th>CCRT (N=35)</th>
<th>RH (N=35)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall LUT symptoms</td>
<td>27 (77.1 %)</td>
<td>23 (71.4 %)</td>
<td>0.78</td>
</tr>
<tr>
<td>Storage symptoms</td>
<td>27 (77.1 %)</td>
<td>22 (62.9 %)</td>
<td>0.30</td>
</tr>
<tr>
<td>Increased daytime frequency</td>
<td>17 (50.0 %)</td>
<td>10 (28.6 %)</td>
<td>0.58</td>
</tr>
<tr>
<td>Nocturia</td>
<td>19 (54.3 %)</td>
<td>10 (28.6 %)</td>
<td>0.05</td>
</tr>
<tr>
<td>Urgency</td>
<td>12 (34.3 %)</td>
<td>8 (22.9 %)</td>
<td>0.43</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>17 (48.6 %)</td>
<td>19 (54.3 %)</td>
<td>0.81</td>
</tr>
<tr>
<td>Urgency incontinence</td>
<td>5 (14.3 %)</td>
<td>1 (2.9 %)</td>
<td>0.20</td>
</tr>
<tr>
<td>Stress incontinence</td>
<td>9 (25.7 %)</td>
<td>13 (37.1 %)</td>
<td>0.44</td>
</tr>
<tr>
<td>Mixed incontinence</td>
<td>3 (8.6 %)</td>
<td>5 (14.3 %)</td>
<td>0.71</td>
</tr>
<tr>
<td>Voiding symptoms</td>
<td>9 (25.7 %)</td>
<td>15 (42.9 %)</td>
<td>0.21</td>
</tr>
<tr>
<td>Straining</td>
<td>3 (8.6 %)</td>
<td>11 (31.4 %)</td>
<td>0.03</td>
</tr>
<tr>
<td>Incomplete emptying</td>
<td>8 (22.9 %)</td>
<td>14 (40.0 %)</td>
<td>0.20</td>
</tr>
<tr>
<td>Poor flow</td>
<td>4 (11.4 %)</td>
<td>10 (28.6 %)</td>
<td>0.13</td>
</tr>
</tbody>
</table>


Similar rates of lower urinary tract (LUT) symptoms but different predominant symptoms

- Storage dysfxn w/ CRT (low bladder compliance, inc bladder sensation)
- Voiding dysfxn w/Rad Hys (high postvoid residual, straining)

<table>
<thead>
<tr>
<th>Urodynamic abnormality</th>
<th>CCRT (N=35)</th>
<th>RH (N=35)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall urodynamic abnormality</td>
<td>21 (60.0 %)</td>
<td>24 (68.6 %)</td>
<td>0.45</td>
</tr>
<tr>
<td>Storage dysfxn</td>
<td>19 (54.3 %)</td>
<td>13 (37.1 %)</td>
<td>0.15</td>
</tr>
<tr>
<td>Low bladder compliance</td>
<td>11 (31.4 %)</td>
<td>3 (8.6 %)</td>
<td>0.05</td>
</tr>
<tr>
<td>Increased bladder sensation</td>
<td>16 (45.7 %)</td>
<td>4 (11.4 %)</td>
<td>0.003</td>
</tr>
<tr>
<td>Reduced bladder sensation</td>
<td>6 (17.1 %)</td>
<td>6 (17.1 %)</td>
<td>0.02</td>
</tr>
<tr>
<td>Detrusor overactivity</td>
<td>6 (17.1 %)</td>
<td>2 (5.7 %)</td>
<td>0.26</td>
</tr>
<tr>
<td>Urodynamic stress incontinence</td>
<td>4 (11.4 %)</td>
<td>5 (14.3 %)</td>
<td>1.00</td>
</tr>
<tr>
<td>Voiding dysfxn</td>
<td>9 (25.7 %)</td>
<td>15 (42.9 %)</td>
<td>0.01</td>
</tr>
<tr>
<td>Decreased flow rate</td>
<td>10 (28.6 %)</td>
<td>11 (31.4 %)</td>
<td>0.79</td>
</tr>
<tr>
<td>High postvoid residual urine</td>
<td>0 (0.0 %)</td>
<td>8 (22.9 %)</td>
<td>0.02</td>
</tr>
<tr>
<td>Voiding with abdominal straining</td>
<td>3 (8.6 %)</td>
<td>10 (28.6 %)</td>
<td>0.05</td>
</tr>
<tr>
<td>Detrusor overactivity</td>
<td>1 (2.8 %)</td>
<td>5 (14.3 %)</td>
<td>0.31</td>
</tr>
</tbody>
</table>


Time Course and Incidence of urinary toxicity in early stage cervical cancer survivors treated with Radiation

1784 stage IB cervical ca pt treated 1960-89

![Graph: Time Course and Incidence of urinary toxicity in early stage cervical cancer survivors treated with Radiation](image)


Physician vs. Patient Assessment of Symptoms – Physicians underestimate patient symptoms

91 cervical cancer survivors with patient and physician-rated morbidity

<table>
<thead>
<tr>
<th>Patient-rated symptoms</th>
<th>None</th>
<th>Mild</th>
<th>Severe</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician-assessed morbidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RW</th>
<th>None</th>
<th>Mild</th>
<th>Severe</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>35</td>
<td>35</td>
<td>21</td>
<td>9</td>
<td>91</td>
</tr>
</tbody>
</table>

Recent Advances that Improve Urinary Toxicity

1. Brachytherapy vs. EBRT for early stage endometrial cancer
2. IMRT vs. 3D for EBRT
3. Image-guided Brachytherapy for Intact Cervical Cancer

Endometrial Cancer

Increasing use of vaginal brachytherapy over pelvic radiation

15-year QOL Post-op RT in Endometrial Cancer (PORTEC-1) Pelvic RT vs. No Additional Therapy

- Median F/u 13.3 yrs, 246 out of 351 surviving patients (714 patients originally)
  - Urinary symptoms
    - EBRT: 47, 21, 37, 21, 0.005
    - IMRT: 43, 27, 35, 27, 0.007
  - Frequency during the night
    - EBRT: 48, 27, 35, 27, 0.007
    - IMRT: 43, 27, 35, 27, 0.007
  - Urinary urgency
    - EBRT: 40, 22, 35, 22, 0.001
    - IMRT: 35, 22, 30, 22, 0.001
  - Sput with dysuria because of urinary symptoms
    - EBRT: 31, 27, 30, 28, 0.001
    - IMRT: 30, 27, 30, 28, 0.001
  - Need to remain close to toilet
    - EBRT: 30, 22, 13, 20, <0.001
    - IMRT: 30, 22, 13, 20, <0.001
  - Incontinence for urine
    - EBRT: 30, 21, 16, 21, <0.001
    - IMRT: 30, 21, 16, 21, <0.001
  - Difficulty with voiding
    - EBRT: 16, 20, 11, 22, 0.001
    - IMRT: 15, 21, 11, 22, 0.001

PORTEC 2 – Pelvic radiation vs. vaginal brachytherapy for early stage, high risk endometrial cancer patients

- Inclusion: ≥ 60 years old
  - Stage IA (<50% invasion) grade 3
  - Stage IB (>50% invasion) grade 1-2
- No difference in vaginal recurrences, OS, DFS
- Significantly less GI toxicity with brachytherapy, compared to EBRT

PORTEC 2 - Health-Related QoL and Cancer Survivorship Outcomes

- 427 patients
- At 7 yr, higher rates of fecal leakage, diarrhea, bowel urgency, and urinary urgency w/EBRT (p=0.03, 0.04, <0.001, 0.05)

3D vs. IMRT for Pelvic Radiation
TIME-C NRG/RTOG Randomized Phase III - 3D vs. IMRT for Post-op Endometrial & Cervical Cancer

- Primary End Pt: Determine if acute GI toxicity reduced with IMRT after 5 wk of treatment using pt reported outcomes
- Secondary:
  › Acute urinary toxicity with pt reported outcomes
  › Quality of life (FACT)

Klopp A et al. JCO 2018

Post-op IMRT - Decreases Late Toxicity

- In a group of 80 uterine and cervix pt, post-op IMRT showed decreased late GI and GU toxicity at 3yr 16% vs. 45% and thereby becomes more cost effective over time.

Chen LA et al. Gyn Onc 2015, 136(3):521-8

Image-Guided Brachytherapy

- 731 cervical cancer patients treated with concurrent chemoRT followed by Image-Guided Brachytherapy (IGBT)
- Improved pelvic control, local control, and OS compared to historical
- Low 5-yr G3-5 morbidity: 5% bladder, 7% GI, 5% vagina

Klopp A et al. JCO 2018

Patient-Reported Bowel and Urinary Outcomes: Standard Radiation (n= 149) vs. IMRT (n= 129)

Klopp A et al. JCO 2018

Intact Cervix IMRT - 135 IMRT vs. 317 non-IMRT
Equivalent Recurrence, Decreased Toxicity

Kidd EA et al. IJROBP 2010, 77(4): 1085-91
Conclusions/Take Home Message

- Treatment of endometrial and cervical cancers often requires radiation, which can cause genitourinary toxicity.
- Gynecologic cancer patients can live many years after their treatment, making long-term urinary tract toxicity a particular concern.
- Recent advances in treatment can help decrease the dose to the bladder and urinary tract.

Outline

- Case introduction
- Background
  - Pathophysiology of radiation-induced bladder dysfunction
  - RTOG classification of genitourinary toxicity
  - Urodynamic changes in lower urinary tract function
- Lower urinary tract dysfunction
  - Acute radio-toxicity
  - Late-phase lower urinary tract complications
  - Evaluation and management
- Case management
- Concluding remarks

Index patient

- Complaint: Mixed urinary incontinence
- 45 year old female with history of cervical cancer s/p radical hysterectomy s/p external beam radiotherapy and chemotherapy s/p high dose brachytherapy 5 years ago. Previously treated with mid-urethral sling, now presents with mesh exposure.

Lower urinary tract dysfunction after pelvic irradiation and radical hysterectomy

LEARNING OBJECTIVE QUESTIONS:

1) What are the most common lower urinary tract dysfunctions in cervical cancer patients >3 years after isolated pelvic radiation?
2) …after isolated radical hysterectomy?
Normal lower urinary tract (LUT) physiology

- Classification of Voiding Dysfunction (Wein, 1981)
  - Failure to store
    - Because of the bladder => Detrusor overactivity / fibrotic small capacity bladder
    - Because of the outlet => Intrinsic sphincter deficiency
  - Failure to empty
    - Because of the bladder => Weak detrusor contraction
    - Because of the outlet => Urethral stenosis / fibrosis
- Radiation induced bladder/outlet dysfunction
  - Pre-existing LUT's often precede radiation
  - Chronic inflammation, impaired wound healing

Bladder dose-volume radio-toxicity

- Bladder only receives partial irradiation during the treatment of gynecologic cancer
  - Lack of knowledge regarding dose-volume bladder radio-toxicity
  - Difficulty to assess the amount of bladder wall receiving dose
  - Variation in bladder filling and shape during irradiation
  - Bladder neck and urethra receive highest radiation dose
- Dose-volume effects (Prostate cancer literature)
  - Less than 5% severe urinary toxicity (< 65 Gy total)
  - 50% severe urinary toxicity (80 Gy total)
  - Increased toxicity with irradiation fraction sizes > 2.0 Gy/fraction

Acute inflammatory phase (< 90 days)

- Loss of GAG layer
- Loss of urothelial cells
- Inflammation
- Edema
- Dilation of blood vessels
- Leaky urothelium
- Bladder neck and urethra receive highest radiation dose
- Radiation induced bladder/outlet dysfunction
  - Pre-existing LUT's often precede radiation
  - Chronic inflammation, impaired wound healing

Loss of uroplakin 30-days after 20 Gy bladder irradiation (mouse)

RTOG classification of genitourinary toxicity: Acute (< 90 days)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Acute (&lt; 90 days)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No change</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Frequency of urination or nocturia twice pre-treatment habit/dysuria, urgency not requiring medication</td>
<td>20-80%</td>
</tr>
<tr>
<td>2</td>
<td>Frequency of urgency that is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anesthesia (e.g., Pyridium)</td>
<td>25%</td>
</tr>
<tr>
<td>3</td>
<td>Frequency with urgency and nocturia hourly or more frequently/dysuria, pelvic pain or bladder spasm requiring regular frequent narcotic/gross hematuria without/with passage</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Hematuria requiring transfusion/acute bladder obstruction not secondary to clot passage, ulceration, or necrosis</td>
<td></td>
</tr>
</tbody>
</table>

Symptoms during the acute phase of radiation

<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>UNDERLYING PATHOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary frequency</td>
<td>Detrusor overactivity</td>
</tr>
<tr>
<td>Urinary urgency</td>
<td>Leaky urothelium</td>
</tr>
<tr>
<td>Dysuria</td>
<td>Intrinsic sphincter deficiency</td>
</tr>
<tr>
<td>Stress urinary incontinence</td>
<td>Poorly compliant bladder</td>
</tr>
<tr>
<td>Urgency urinary incontinence</td>
<td>Fistula</td>
</tr>
<tr>
<td>Mixed urinary incontinence</td>
<td>Ureteral stricture</td>
</tr>
<tr>
<td>Microscopic and gross hematuria</td>
<td>Urethral stricture</td>
</tr>
<tr>
<td>Radiation cystitis</td>
<td></td>
</tr>
</tbody>
</table>

Most acute symptoms are self-limiting and independently managed by the radiation oncologist
Treatments during the acute phase of radiotherapy

- Standard Treatments
  - Pyridium
  - Anticholinergics
  - Hydration

- Clinical Investigational
  - Intravesical instillations
    - Chondroitin sulfate
    - Sodium hyaluronate

- Basic Science Investigational
  - Myofibroblast detrusor injections
  - Muscle derived progenitor cells
  - Intravesical liposomal tacrolimus

Patients with baseline LUTS are more likely to experience exacerbation of symptoms.

Latent recovery phase (Months-Years)

- Endarteritis
- Urothelial proliferation
- Leaky urothelium?

50% recovery of uroplakin around 100-days after 20 Gy bladder irradiation (mouse)

Late chronic phase (Years-Decades)

- Increased collagen deposition
- Fibroblast infiltration
- Loss of smooth muscle cells
- Endarteritis
- Edema
- Hemorrhage
- Chronic inflammation

Fibrosis

Poor bladder compliance and chronic inflammation at 6 months after radiation (rat)

RTOG classification of genitourinary toxicity: Late / Chronic

<table>
<thead>
<tr>
<th>Grade</th>
<th>Late / Chronic</th>
<th>%</th>
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<tbody>
<tr>
<td>0</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Slight epithelial atrophy; minor telangiectasia (microscopic hematuria)</td>
<td>45% (5 years)</td>
</tr>
<tr>
<td>2</td>
<td>Moderate frequency; generalized telangiectasia; intermittent macroscopic hematuria</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Severe frequency and dysuria; severe telangiectasia (often with petechiae); frequent hematuria; reduction in bladder capacity (&lt; 150 cc)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Necrosis Contracted bladder (capacity &lt; 100 cc); severe hemorrhagic cystitis</td>
<td></td>
</tr>
</tbody>
</table>
Chronic radiation induced lower urinary tract complications in the female

<table>
<thead>
<tr>
<th>SYMPTOM</th>
<th>UNDERLYING PATHOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary frequency</td>
<td>Detrusor overactivity</td>
</tr>
<tr>
<td>Urinary urgency</td>
<td>Leaky urethral</td>
</tr>
<tr>
<td>Dysuria</td>
<td>Intrinsic sphincter deficiency</td>
</tr>
<tr>
<td>Stress urinary incontinence</td>
<td>Poorly compliant bladder</td>
</tr>
<tr>
<td>Urgency urinary incontinence</td>
<td>Fistula</td>
</tr>
<tr>
<td>Mixed urinary incontinence</td>
<td>Urethral stricture</td>
</tr>
<tr>
<td>Straining</td>
<td>Urinary stricture</td>
</tr>
<tr>
<td>Microscopic and gross</td>
<td>Radiation cystitis</td>
</tr>
</tbody>
</table>

What are the most common LUT dysfunctions after pelvic radiation?

LUT dysfunction after chemoradiation (CCRT) versus radical hysterectomy (RH)

<table>
<thead>
<tr>
<th>Urodynamic Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation = Storage dysfunction</td>
</tr>
<tr>
<td>Urinary frequency</td>
</tr>
<tr>
<td>Urinary urgency</td>
</tr>
<tr>
<td>Dysasia</td>
</tr>
<tr>
<td>Stress urinary incontinence</td>
</tr>
<tr>
<td>Urgency urinary incontinence</td>
</tr>
<tr>
<td>Mixed urinary incontinence</td>
</tr>
<tr>
<td>Straining</td>
</tr>
</tbody>
</table>

Principles of evaluation

- Minimum evaluation - careful history, physical exam, and urinalysis
  - History related to cancer
    - Dose, timing and route of irradiation
    - Concomitant pelvic surgery
    - Disease status and expected survival
  - Review of systems
    - Recurrent UTI, hematuria, bowel symptoms, fecaluria
  - Assess co-morbid conditions
    - Diabetes, neurologic conditions, aging
    - History of mesh / incontinence surgery
  - AD discretion - urine culture, bladder diaries, uroflow/PVR
  - Complicated patient - cystoscopy, renal-bladder ultrasound
  - Urodynamics considered when invasive, potentially morbid or irreversible treatments are considered.

Principles of treatment

- Lower urinary tract dysfunction following pelvic radiation is rarely life threatening (with the exception of hemorrhagic cystitis)
- Treatment expectations should be guided by patient's degree of bother and impact on quality of life
- Patients should understand that radiation induced bladder dysfunction is progressive and often irreversible

Impaired wound healing - Vaginal synthetic/permanent implants should be avoided in most cases after radiation.
Bladder and outlet treatments during the end-stage chronic phase of radiotherapy (RTOG Grade 3-4)
Continent vs. Incontinent Urinary diversion +/- cystectomy

<table>
<thead>
<tr>
<th>Author</th>
<th>Cohort</th>
<th>Follow Up</th>
<th>Objective Findings/Subjective Findings</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilkin (2005)</td>
<td>N = 26 (N = 12 prior RT); series Indiana pouch at time of extent for recurrent gyn. cancer</td>
<td>12 months (minimum), 48.5 months (mean), prior RT group</td>
<td>89% of 12 patients had one or more complications</td>
<td>30 months interval between RT and surgery</td>
</tr>
<tr>
<td>Al Hussein Al Awamlh (2015)</td>
<td>N = 29; Case series cystectomy and diversion after pelvic RT (N = 5 women)</td>
<td>37.3 months (median) NR</td>
<td>65.5% 30- day postoperative complications</td>
<td>87 month (median) interval between RT and 1st symptoms</td>
</tr>
<tr>
<td>Banerji (2015)</td>
<td>N = 28; Case series ileal conduit after cervical cancer RT (N = 18 vesico-vaginostomy)</td>
<td>13.2 months (mean) NR</td>
<td>Global Impression of Change Scale 5.2/7 (vs. 3/7 w/o conduit, p = 0.06)</td>
<td>9.8 year (mean) interval between RT and cystitis</td>
</tr>
</tbody>
</table>

**Index patient**

- **LEARNING OBJECTIVE QUESTIONS:**
  1. What are the most common lower urinary tract dysfunctions in cervical cancer patients >3 years after isolated pelvic radiation?
  2. …after isolated radical hysterectomy?

**Pelvic Radiation**
- Storage dysfunction
- Poorly compliant bladder
- Increased bladder sensation

**Radical Hysterectomy**
- Voiding dysfunction
- High post void residual
- Voiding with abdominal straining
- Increased bladder capacity
- Weakened detrusor

**Take home message**

- Management of the acute and long term adverse effects of radiation induced bladder dysfunction can be complicated and frustrating.
- Since chronic radiation damage is generally irreversible, the available treatment options are primarily palliative and should be focused on symptom management.

**DISCUSSION**

- Radiation induced vaginal dysfunction
- Workshop # W9, International Continence Society Annual Meeting, Philadelphia
- Tuesday, August 28th, 2018
Gynecologic malignancies and targeted treatment locations

- Fallopian tube
- Uterus
- Ovary
- Cervix
- Vagina
- Labium major
- Near-SV Continual Sense
- Near-SV Continual Sense

Radiation-induced pelvic floor and vaginal dysfunction in cervical and endometrial cancer survivors

Workshop # W5, International Continence Society Annual Meeting, Florence, Italy
Tuesday, September 12th, 2017

BERTHA CHERN, M.D.
STANFORD UNIVERSITY
DEPARTMENT OF OBSTETRICS & GYNECOLOGY
STANFORD, CALIFORNIA, USA

relationship between exposure to XRT and PFDs in endometrial cancer survivors

<table>
<thead>
<tr>
<th>PFD</th>
<th>No XRT (n=87)</th>
<th>XRT (n=62)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mod-severe UI</td>
<td>24 (27.7%)</td>
<td>14 (22.6%)</td>
<td>0.78</td>
</tr>
<tr>
<td>SUI</td>
<td>21 (24.1)</td>
<td>13(21.0)</td>
<td>0.81</td>
</tr>
<tr>
<td>UII</td>
<td>23(26.4)</td>
<td>8(13)</td>
<td>0.33</td>
</tr>
<tr>
<td>POP</td>
<td>3(3.4)</td>
<td>4(6.5)</td>
<td>0.38</td>
</tr>
<tr>
<td>Fecal Incontinence</td>
<td>42(48.3)</td>
<td>28(45.2)</td>
<td>0.66</td>
</tr>
<tr>
<td>Sexual function score PISQ-12 (median, IQR)</td>
<td>32(16-38)</td>
<td>21 (0-34)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Segal S et al. Maturitas. 2017.03.313

Vaginal changes after pelvic radiation therapy

- "Radiation vaginitis" – vaginal discharge, spontaneous and contact bleeding, and dyspareunia
- Cellular damage followed by inflammation, erythema, moist desquamation/mucositis
- The inflammation causes formation of adherences between the vaginal walls and obliteration of the vagina
- Loss of vaginal elasticity and stenosis due to fibrosis
- Loss of ovarian function resulting in decreased lubrication
- Late toxicity – 18-32% of patients


Sexual function - addressed in ICS 2015 Roundtable presentation – Dr. Shauna Correia, Pelvic floor dysfunction in cancer survivors after radical pelvic surgery and radiation therapy
https://www.ics.org.tv?play=9327

Case – Radiation induced vaginal dysfunction

- >90 year old with history of endometrial cancer.
- Treated with surgical staging and external beam radiation in 1980’s
- Near-term vaginal sequela : vaginal shortening and stenosis, vaginal dryness, eventual coaptation of the remaining vagina ---- not sexually active since her 40’s
- Long term issues: urinary incontinence, both ISD and underactive bladder, and nocturia.

Genitourinary syndrome of menopause (loss of ovarian function)

- Vagina: stratified squamous, non-keratinized epithelium sensitive to estrogen deprivation
- Lack of estrogen: thinning of epithelium, dryness, inflammation, loss of elasticity, change in flora, decreased blood flow, increased pH, narrowing of vaginal canal, labial agglutination, labial fat pads diminish


Sexual function - addressed in ICS 2015 Roundtable presentation – Dr. Shauna Correia, Pelvic floor dysfunction in cancer survivors after radical pelvic surgery and radiation therapy
https://www.ics.org.tv?play=9327
The radiated vagina > one year after pelvic XRT

Epithelium - thin with loss of intermediate and superficial layers
Lamina propria - Hyalinization and collagenization
Muscular layer - smooth muscle fibers are replaced by fibrotic tissue


Treatment characteristics of survivors with and without loss of vaginal elasticity

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Survivors with loss of elasticity</th>
<th>Survivors without loss of elasticity</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>55 (25-80)</td>
<td>42 (25-70)</td>
<td>0.09</td>
</tr>
<tr>
<td>Stage</td>
<td>III (1)</td>
<td>I (1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Tumor size</td>
<td>10 cm (5-15)</td>
<td>5 cm (3-10)</td>
<td>0.05</td>
</tr>
<tr>
<td>Metastasis</td>
<td>No (4)</td>
<td>Yes (1)</td>
<td>0.03</td>
</tr>
<tr>
<td>Treatment</td>
<td>Surgery, chemotherapy, hormonal</td>
<td>Surgery, chemotherapy, hormonal</td>
<td></td>
</tr>
<tr>
<td>Dose (cGy)</td>
<td>6000 (5500-6500)</td>
<td>4500 (4000-5000)</td>
<td></td>
</tr>
</tbody>
</table>

Alevronta E et al. Radiotherapy and Oncology 120(2016) 537-541

Sexual dysfunction after gynecological radiation therapy

- 34% of patients report loss of vaginal elasticity compared to 14% in controls
- Late complications might be lifelong
- Mean absorbed dose to the vagina and AGE of patient are significantly risk factors
- 50-60% prevalence of dyspareunia
- 48% reported a smaller vaginal dimension at 12 months

Distribution of superficial and deep dyspareunia after pelvic XRT


Cellular changes in the vaginal in response to estrogen and radiotherapy

- Acute radiation vaginitis is managed with topical intravaginal estrogens
- Irradiation has an inhibitory effect on cellular division with resulting reduction in thickness of epithelium
- Estrogen increases mitosis and proliferation of vaginal basal cells

Vaginal histology grade changes with estrogen use after radiation therapy


Stanford University
Treatment of vaginal dysfunction after radiation

- Mainstay of therapy:
  - Vaginal dilator
    - May consider topical anesthetic, if necessary
  - Vaginal estrogen
    - Non-hormonal therapy if estrogen contraindicated
- Duration of therapy is variable
  - Range 2-8 months
- Pelvic Floor PT

Vaginal dilator – Cochrane review 2014

- Two RCTs – no improvement in sexual scores associated with dilation therapy
- Vaginal length increased by mean of 3cm after dilation was introduced 6-10 weeks after XRT (no control group)
- Several studies showed less stenosis associated with prophylactic dilation, one case series showed the opposite
- Conclusion from the review – there is no reliable evidence to show that routine vaginal dilation prevents stenosis or improves quality of life. While there is an associating between vaginal dilation and less stenosis, but this does not prove that the benefit is due to dilation. RCT methodology is challenging in this area

Special considerations on estrogen therapy and vaginal dilation

- Unclear whether dilation or estrogen therapy have an effect on the fibrosis resulting long term after radiotherapy
- Transvaginal absorption of estrogens through irradiate vagina is high (>80 fold in mean serum E2 increase with micronized E2 vaginal administration)

Vaginal moisturizers (non-hormonal)

- Non-prescription, long-term relief of vaginal dryness
- Replenish water content to vagina, improves elasticity
- Longer duration of effect than personal lubricants
- Often used for the treatment of atrophic vaginitis (vaginal dryness, itching)

Lubricants: water-based

- Most widely available
- Safe to use with latex condoms, sex toys
- Tend to dry up quickly
  - Reactivate with water
- Do not stain
- Rarely cause irritation
- Common ingredients:
  - Deionized water, glycerin, propylene glycol
  - Available in glycerin-free options
  - Glycerin may promote vaginal inflammation and yeast infection
  - K-Y, Pink Water, Liquid Silk, Pjur, Siquid

Lubricants: silicone-based

- Longer lasting than water-based lubricants
- Can be used in water
- Safe to use with latex condoms, diaphragms, non-silicone toys
- Available in glycerin-free options
- Can be used as a massage oil
- More expensive than water-based lubricants
- Harder to wash off sheets and clothing
- Pjur Original Bodyglide, Astroglide X, Wet Platinum, Pink Silicone
Lubricants: oil-based

- Petroleum-based:
  - Petroleum jelly, mineral oil, baby oil
  - May promote vaginal inflammation/irritation
  - Not for use with latex condoms
  - Can reduce both the effectiveness of latex items and prevention of STDs

- Natural oils:
  - Coconut, avocado, corn, olive, peanut
  - Non-irritating
  - Should not be used with latex items

Vaginal moisturizers

- Long-term efficacy and safety is unknown
  - Most studies do not look beyond 3 months

- Placebo effect/transient benefit?
  - Vaginal moisturizer improved VSS at week 4 (p = 0.01), but score returned to pre-treatment values at week 12; no significant modification of VHI

Vaginal lubrication - laser vaginal therapy

There is currently NO data on the safety of laser vaginal therapy for radiation induced vaginal dryness and dyspareunia. It is NOT FDA approved for these indications

How to counsel patients...

- Urinary incontinence
  - 70% vs 56% moderate UI (Rutledge et al, 2010)
  - Significant association with UI (p<.01) PORTEC-1 trial
  - No significant difference between EBRT and VBT PORTEC-2 trial
  - No significant association (Segal 2017) Age and BMI are significant risk factors for UI

- Fecal incontinence
  - 42% vs 32% (p=.02) (Rutledge et al, 2010)
  - Significant association with FI PORTEC-1 trial
  - 10.6% EBRT vs. 1.8% VBT (p=.04) PORTEC-2 trial
  - No significant association (Segal 2017)

- Pelvic organ prolapse
  - Numbers too small (Segal 2017)
  - Case reports

- Sexual dysfunction
  - Significant association (Segal 2017)

Back to Case – Radiation induced vaginal dysfunction

- >90 year old with history of endometrial cancer
- Treated with surgical staging and external beam radiation in 1980’s
- Near-term vaginal sequela: vaginal shortening and stenosis, vaginal dryness, eventual coaptation of the remaining vagina ---- not sexually active since her 40’s
- Long term issues: urinary incontinence, both ISD and underactive bladder, and nocturia

Radiation and surgery for pelvic floor disorders

- Series of 78 patients with cervical cancer with complete uterine prolapse (Matsuo K et al, Int Urogynecol J, 2016). Surgery-based therapy was associated with improved disease-specific overall survival rate
- Vaginal vault dehiscence and used of vaginal vault brachytherapy (Wiebe E et al, Int J Gynecol Cancer 2012)
**Take Home Message**

- Radiation induced pelvic floor and vaginal dysfunction is common.
- Awareness, early identification of the problem by the medical team, and early institution of treatment can help increase cancer survival wellbeing.
  - Early institution of vaginal dilation
  - PFT
  - Vaginal lubricants (silicon-based)
- Vaginal mesh treatments may have decreased efficacy and increased risks
- Prolapse may undergo spontaneous reduction after pelvic XRT
- Clinical studies are needed to direct therapy

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**Physiotherapy of the radiated pelvic floor**

- Stephanie Bernard, PhD(c), PT
- Université Laval, Québec, Canada

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**Physiotherapy for the Treatment of Radiation Induced Pelvic Floor Dysfunction**

- Case introduction
- Evaluation of the radiated pelvic floor
  1. Assessment of pelvic floor musculature
- Pelvic floor physiotherapy approaches for the radiated pelvic floor
  1. Pelvic floor exercises
  2. Dilation therapy
- Case management
- Conclusion

---

**Case presentation – Ms. J**

- 39 y.o.
- Endometrial cancer stage 1B, 48 months ago;
- Surgery (TAH+BSO) and 21 Gray of vaginal brachytherapy (VBT);
- Single, nulliparous, BMI: 27.4, currently not sexually active;

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**Case presentation**

- Reason for pelvic floor PT consult:
  - Increased voiding frequency,
  - Straining during voiding,
  - Urinary urgency and mixed urinary incontinence for > 2 years.

---

**Physiotherapy assessment**

- Medical history
- Symptom history
- Goals
- Impact on sleep, work, leisure activities
- Vaginal/vulvar soft tissue mobility
- Pain, hip and lumbar function
- Sexual function, dyspareunia
Assessment of the pelvic floor muscles (PFMs)

**PFM assessment**
- Contractility
- Muscle tone and structure

**Assessment of the pelvic floor muscles (PFMs)**

• PFM clinical assessment of contractility
  - Digital (PERFECT)\(^1,2\)
    - Strength
    - Endurance
    - Speed
  - Ultrasound

- Digital
- Ultrasound\(^{16}\)

**Assessment of the PFMs**

How is contractility impaired after irradiation?

- 2/13 studies after gynecological cancer \(^4,5\)
- ↓ pressure at anal sphincter (rest and max contraction)
- ↓ # women presenting strong strength values
Assessment of the PFMs

How is contractility impaired after irradiation?

Pelvic-Floor Dysfunction Special Issue

Pelvic-Floor Properties in Women Reporting Urinary Incontinence After Surgery and Radiotherapy for Endometrial Cancer

Stephen M. Newhouse, Michelle Neves, Marie-France Poirier, Marie-Franoise Desjardins, Marie-Hélène Charbonneau, Sylvie Côté, Séverine Gagnon, Yvan L. Gagné

Assessment of the PFMs

How is contractility impaired after irradiation?

Women after RT and TAH+BSO presented with:

➢ ↓ maximal strength and force development
➢ ↓ number of rapid contractions
➢ No difference in endurance

What about tone?

Women after RT and TAH+BSO presented with:

➢ ↓ maximal strength and force development
➢ ↓ number of rapid contractions
➢ No difference in endurance

Assessment of the PFMs

How is muscle tone/anatomical structure impaired after irradiation?

➢ Systematic review: No change in anal sphincter thickness on anal ultrasound

Assessment of the PFMs

How is muscle tone/structure impaired after irradiation?

➢ Cross-sectional study: ↓ antero-posterior opening at vaginal entry
➢ Also decreased vaginal length compared to hysterectomy alone.

Why does it matter?

How are PFM tone, structure and contractility related to urinary function?

➢ PFM and UI:
  • ↓ max strength, rapid contractions, endurance and tone of the PFM,7,8
➢ UI in endometrial cancer survivors:
  • Poor performance in endurance and speed tests, and shorter vaginal length,6

Case presentation

➢ PFM contractility:
  • Strength: 4/5 (Oxford scale), 4-5 sec hold
  • Poor repeatability: 4 x max strength
  • Poor control during quick contractions

➢ PFM tone:
  • Stiffness (+2 Reissing digital scale)
Pelvic floor physiotherapy approaches

1. Exercises
2. Manual and dilation therapy
3. Bladder training

1. Exercises for the irradiated PFM

The main goal is to improve PFM contractile function in order to:
- Reduce symptoms of SUI
- Prevent leakage during urgency
- Any bowel continence issues

Intensive programs have better results in women with UI:
- 5x/week
- 10 minutes/day
- Various exercises and body positions
- Techniques to enhance adherence to (exercise diaries, goal-setting, audio or visual aids for home training, etc.)

2. Manual and dilation therapy

Main goals for dilation therapy:
- Prevent vaginal adhesions and stenosis
- Facilitate sexual intercourse
- Facilitate medical assessment of the vaginal canal
- Improve PFM passive mobility and function
- Reduce UI?

Prevention and improvement of the mobility and dimension of the vaginal canal:
- Progressive increase in size (digital, small to bigger dilators)
- Gentle, progressive insertions (depth)
- Static holds to maximum 10 min
2. Manual and dilation therapy

Prevention and improvement of PFM mobility and function:
- Slow, gentle stretch into the PFMs, static holds in various directions
- Massage the PFMs
- Use smaller and more flexible (silicone) dilators, or fingers

2. Manual and dilation therapy

Recommandations:
- Begin 2-8 wks after RT
- Always use recommended lubricant
- 3 times a week during 1st year
- Up to 2 years after RT

Precautions:
- Avoid using during inflammatory phase
- Recognize psychological distress in regards to the use of dilators
- Small, non-recurrent bleeding is normal, but avoid repetitive vaginal trauma and pain.

2. Dilators: do they work?

➢ Cochrane review Miles 2014: «... no reliable evidence to show that routine, regular vaginal dilation during radiotherapy treatment prevents stenosis or improves quality of life.»
➢ Law 2015: Women with higher adherence (6 months) to dilator therapy associated with maintaining/returning to pre-RT size.
➢ No study on effect of dilation therapy on PFM function/continence

3. Bladder training

Main goals for bladder training:
- Reduce voiding frequency
- Improve bladder emptying
- Decrease urinary urgency

➢ The (additional) benefits of bladder training in women with UI after gynacological cancer is unknown
➢ As MUI is frequent in this population, it should be considered as a possible important component of a conservative rehabilitation program.
Case presentation

Month 1:
- In clinic: manual therapy to the PFM, biofeedback for training contractility exercises, bladder training (water consumption, voiding diary)
- At home: dilation therapy (static) and PFM exercises

Month 2:
- PFM training for urge suppression
- Mindfulness exercises for awareness of bladder sensations
- Dilation therapy: dynamic stretches at home

Month 3:
- As most symptoms were controlled, plan for long-term adherence (maintenance PFM exercise program, dilation therapy 1 to 2x/week and maintenance of voiding habits) with telephone follow-up.

References
References


**DISCUSSION**