W9: Radiotherapy of cervical and endometrial cancer – Prevention and management of lower urinary tract, vaginal, vulvar and pelvic floor dysfunction in cancer survivors

Workshop Chair: Amy Dobberfuhl, United States
28 August 2018 11:00 - 12:30

Start	End	Topic	Speakers
11:00	11:20	Minimizing radio-toxicity to benign tissues (Radiation Oncologist)	Elizabeth Kidd
11:20	11:40	Acute and chronic lower urinary tract dysfunction (Urologist)	Amy Dobberfuhl
11:40	11:45	Discussion	Amy Dobberfuhl Elizabeth Kidd
11:45	12:05	Radiation induced vaginal dysfunction (Urogynecologist)	Bertha Chen
12:05	12:25	Physiotherapy of the radiated pelvic floor (Pelvic Floor Physiotherapist)	Stephanie Bernard
12:25	12:30	Discussion	Bertha Chen Stephanie Bernard

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

1) De Boer SM, et al. Long-Term Impact of Endometrial Cancer Diagnosis and Treatment on Health-Related Quality of Life and Cancer Survivorship: Results From the Randomized PORTEC-2 Trial. Int J Radiat Oncol Biol Phys. 2015, 93(4):797-809 PMID: 26530748.
2) Katepratoom C, et al. Lower urinary tract dysfunction and quality of life in cervical cancer survivors after concurrent chemoradiation versus radical hysterectomy. Int Urogynecolol J 2014, 25(1): 91-6. PMID: 23818129.

3) Vistad I, et al. Postradiotherapy morbidity in long-term survivors after locally advanced cervical cancer: how well do physicians' assessments agree with those of their patients? Int J Radiat Oncol Biol Phys. 2008, 71(5):1335-42. PMID: 18355976.
4) Zwaans BM, Chancellor MB, Lamb LE. Modeling and Treatment of Radiation Cystitis. Urology. 2016 Feb;88:14-21. PMID: 26571081.
5) Payne H, et al. Chemical- and radiation-induced haemorrhagic cystitis: current treatments and challenges. BJU Int. 2013 Nov;112(7):885-97. PMID: 24000900.
6) Rajaganapathy BR, et al. Advances in Therapeutic Development for Radiation Cystitis. Low Urin Tract Symptoms. 2014 Jan;6(1):1-10. PMID: 26663493.
7) Bernard S, et al. Effects of radiation therapy on the structure and function of the pelvic floor muscles of patients with cancer in the pelvic area: a systematic review. J Cancer Surviv. 2016 Apr;10(2):351-62. PMID: 26314412.
8) Bernard S, et al. Pelvic-Floor Properties in Women Reporting Urinary Incontinence After Surgery and Radiotherapy for Endometrial Cancer. Phys Ther. 2017; 97: 438-448. PMID: 28201796.

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 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.

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.

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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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2018 International Continence Society Annual Meeting, Philadelphia, USA
Tuesday, August 28th, 2018

ICS 2018 PHILADELPHIA

Affiliations to disclose†:

Elizabeth Kidd (none)
Amy Dobberfuhl (NIH 5KL2TR001083, 1L30DK115056)
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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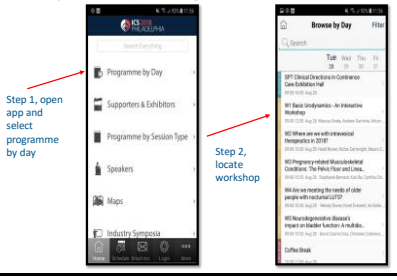
WIN $150 AMAZON VOUCHERS

Please complete the in-app evaluation in the workshop before leaving.



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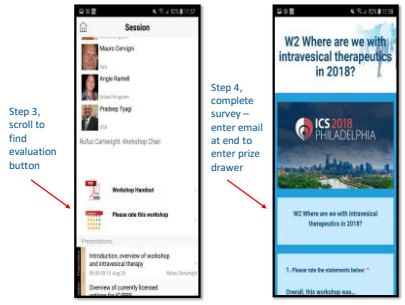

ICS 2018 PHILADELPHIA

- 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.

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OVERVIEW

Aims of Workshop

ICS 2018 PHILADELPHIA

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

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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

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Stanford MEDICINE

Minimizing Radiation Toxicity to Benign Tissues

ELIZABETH KIDD, M.D.
STANFORD UNIVERSITY SCHOOL OF MEDICINE
DEPARTMENT OF RADIATION-ONCOLOGY
STANFORD, CALIFORNIA, USA

Workshop # W9, International Continence Society Annual Meeting, Philadelphia
Tuesday, August 28th, 2018

Outline/ Overview

- Example case and background on:
  - Radiation treatment used for managing endometrial and cervical cancer
  - Types of urinary toxicity from pelvic and brachytherapy radiation and time course
- Recent data on ways of decreasing urinary toxicity

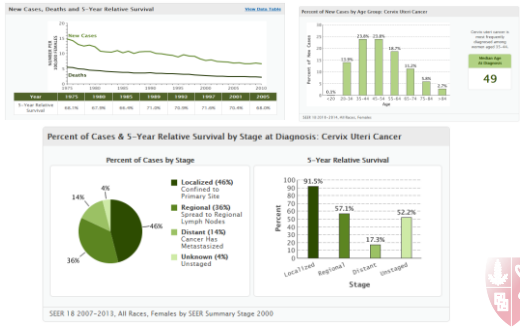
Example case

- 2007 – 34 yo G2P2 woman presents with a FIGO stage IB1 cervical squamous cell carcinoma
  - Initial imaging showed enlarged pelvic LN, confirmed metastases with LN dissection (no hysterectomy)
- Treated with concurrent cisplatin, pelvic radiation and tandem & ovoid brachytherapy
  - Noticed hot flashes and stop of menses shortly after completing treatment
- Followed with clinical exam, interval imaging

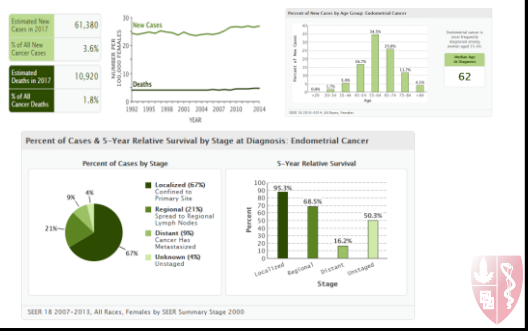
Example case (continued)

- 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

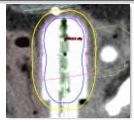


Endometrial Cancer Background

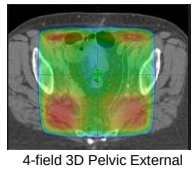


Endometrial Cancer – Types of radiation given

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



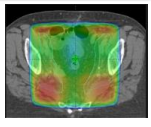
Vaginal Cylinder Brachytherapy



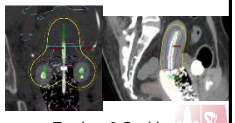
4-field 3D Pelvic External Beam Radiation

Cervical Cancer – Types of radiation given

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

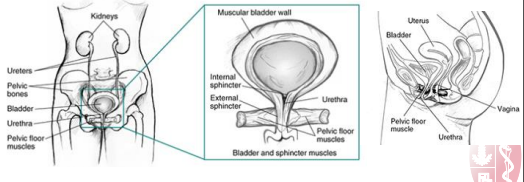


Pelvic External Beam Radiation

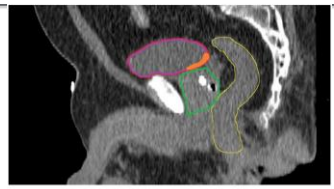


Tandem & Ovoid Brachytherapy

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 chemoRT (EBRT + Brachy) vs. type III Rad Hys (no pre or post-op RT)
- More advance stage in CRT

Characteristics	CCRT (*N*=35)	RH (*N*=35)	*P* value
Mean age (years) ± SD (range)	55.1±9.4 (42–77)	51.6±8.2 (38–69)	0.10
Mean age at treatment (years) ± SD (range)	49.0±9.3 (36–72)	46.3±7.6 (28–59)	0.18
Mean post-treatment interval (years) ± SD (range)	5.8±2.8 (3–13)	5.7±3.5 (3–14)	0.88
Median parity (range)	2 (0–10)	2 (0–6)	0.44

Katepratatoom C et al. Int Urogynecol J 2014, 25: 91-96

Similar rates of lower urinary tract symptoms but different predominant symptoms

LUT symptoms	CCRT (*N*=35)	RH (*N*=35)	*P* value
Overall LUT symptoms	27 (77.1 %)	25 (71.4 %)	0.78
Storage symptoms	27 (77.1 %)	22 (62.9 %)	0.30
Increased daytime frequency	7 (20.0 %)	10 (28.6 %)	0.58
Nocturia	19 (54.3 %)	10 (28.6 %)	0.05
Urgency	12 (34.34 %)	8 (22.9 %)	0.43
Urinary incontinence	17 (48.6 %)	19 (54.3 %)	0.81
Urgency incontinence	5 (14.3 %)	1 (2.9 %)	0.20
Stress incontinence	9 (25.7 %)	13 (37.1 %)	0.44
Mixed incontinence	3 (8.6 %)	5 (14.3 %)	0.71
Voiding symptoms	9 (25.7 %)	15 (42.9 %)	0.21
Straining	3 (8.6 %)	11 (31.4 %)	0.03
Incomplete emptying	8 (22.9 %)	14 (40 %)	0.20
Poor flow	4 (11.4 %)	10 (28.6 %)	0.13

Katepratatoom C et al. Int Urogynecol J 2014, 25: 91-96

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)

Urodynamic abnormality	CCRT (*N*=35)	RH (*N*=35)	*P* value
Overall urodynamic abnormality	21 (60 %)	24 (68.6 %)	0.45
Storage dysfunction	19 (54.3 %)	13 (37.1 %)	0.15
Low bladder compliance	11 (31.4 %)	3 (8.6 %)	0.03
Increased bladder sensation	16 (45.7 %)	4 (11.4 %)	0.003
Reduced bladder sensation	0 (0 %)	6 (17.1 %)	0.02
Detrusor overactivity	6 (17.1 %)	2 (5.7 %)	0.26
Urodynamic stress incontinence	4 (11.4 %)	5 (14.3 %)	1.00
Voiding dysfunction	9 (25.7 %)	18 (51.4 %)	0.03
Decreased flow rates	10 (28.6 %)	11 (31.4 %)	0.79
High postvoid residual urine	0 (0 %)	6 (17.1 %)	0.02
Voiding with abdominal straining	3 (8.6 %)	11 (31.4 %)	0.03
Detrusor underactivity	1 (2.8 %)	5 (14.3 %)	0.11

Katepratatoom C et al. Int Urogynecol J 2014, 25: 91-96

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

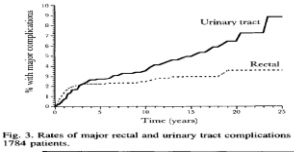


Fig. 3. Rates of major rectal and urinary tract complications in 1784 patients.

Complication	Highest grade 1	2	3	4	5	Total Grades 1–5	Total Grade ≥ 3	Actuarial risk of grade ≥ 3 (%) 5-yr	10-yr	20-yr
All urinary tract	86	44	31	35	6	202	72	2.6	3.3	6.2
Hematuria	67	24	24		1	116	25	1.0	1.4	2.3
Dysuria	36	28	4			68	4			
Bladder fistula		1	2	16	2	21	20	0.7	0.9	1.6
Ureteral stricture	6	8	7	19	3	43	29	1.0	1.2	2.5

Eifel P et al. Int J Rad Onc Biol Phys 1995, 32(5):1289-1300

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

91 cervical cancer survivors with patient and physician-rated morbidity

	Patient-rated symptoms: Bladder			
Physician- assessed morbidity	None	Mild	Severe	Total
None	27 (45%)	23 (38%)	10 (17%)	60 (100%)
Grade 1–2	8	12	9	29
Grade 3–4	0	0	2	2
Total	35	35	21	91

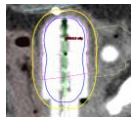
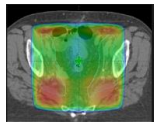
Vistad I et al. Int J Rad Onc Biol Phy 2008, 71(5):1335-42

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

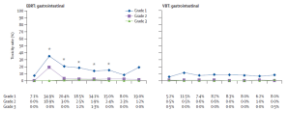
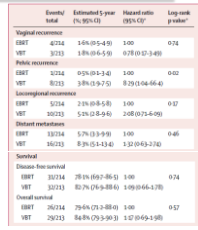
- Median F/u 13.3. yrs, 246 out of 351 surviving patients (714 patients originally)

Urinary symptoms	EBRT (n = 113)	NAT (n = 133) Mean ± SD	P*
Frequency during the day	47 ± 31	37 ± 31	.015
Frequency during the night	48 ± 27	39 ± 27	.017
Urinary urgency	**46 ± 33**	**32 ± 32**	**.001**
Sleep deprivation because of urinary symptoms	21 ± 27	20 ± 30	.716
Need to remain close to toilet	**26 ± 32**	**10 ± 20**	**< .001**
Incontinence for urine	**30 ± 31**	**16 ± 23**	**< .001**
Dysuria	6 ± 16	6 ± 16	.810
Difficulty with voiding	16 ± 25	11 ± 22	.121
Limitation of daily activities because of urinary symptoms	**11 ± 21**	**4 ± 13**	**.006**

Nout RA et al. JCO 2011, 29(13):1692-1700

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

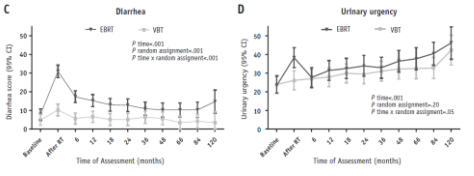
- Inclusion: ≥ 60 years old
  - Stage IA (<50% invasion) grade 3
  - Stage IB (>50% invasion) grade1-2
- No difference in vaginal recurrences, OS, DFS
- Significantly less GI toxicity with brachytherapy, compared to EBRT

Nout RA et al. Lancet 2010, 375:816-23

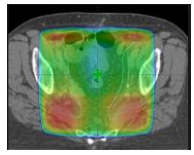
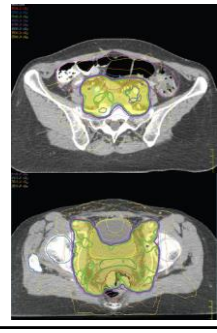
PORTEC 2 - Health-Related QoL and Cancer Survivorship Outcomes

- 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)



Int J Radiation Oncol Biol Phys, Vol. 93, No. 4, pp. 797–809, 2015

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

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

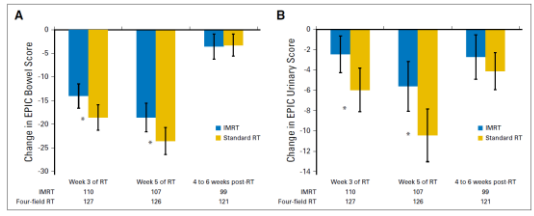


Fig 2. Expanded Prostate Cancer Index Composite (EPIC) assessment of toxicity. Changes in EPIC (A) bowel, and (B) urinary summary scores between baseline and week 3 of radiation therapy (RT), week 5 of RT, and 4 to 6 weeks after completion of RT. Higher scores reflect better function so that greater declines are seen in patients with increased burden of symptoms. Error bars represent 95% CIs. (*) Statistically significant difference. IMRT, intensity-modulated radiation therapy.

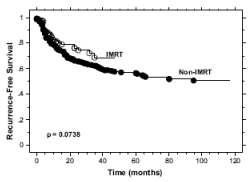
Klopp A et al. JCO 2018

Post-op IMRT - Decreases Late Toxicity

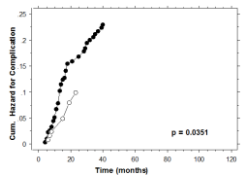
- In a group of 80 uterine and cervix pt, post-op IMRT showed decreased late GI and GU toxicity at 3yr 16% vs. 45% and thereby becomes more cost effective over time.

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

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



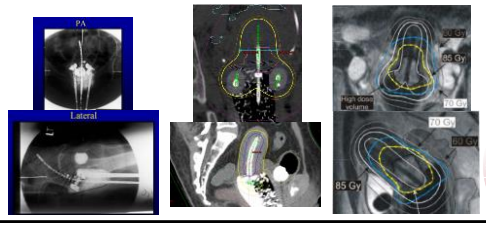
Recurrence-Free Survival



Grade 3 or greater GI & GU toxicity

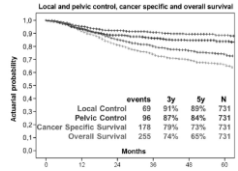
Kidd EA *et al.* IJROBP 2010, 77(4): 1085-91

Image-Guided Brachytherapy




Radiotherapy and Oncology
Image guided brachytherapy in locally advanced cervical cancer: Improved pelvic control and survival in RetroEMBRACE, a multicenter cohort study

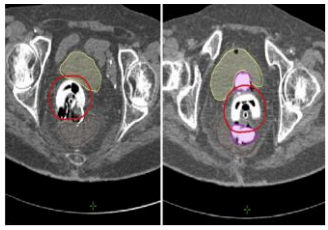
- 731 cervical cancer patients treated with concurrent chemoRT followed by Image-Guided Brachytherapy (IGBT)
- Improved pelvic control, local control, and OS compared to historical
- Low 5-yr G3-5 morbidity: 5% bladder, 7% GI, 5% vagina



ELSEVIER
BRACHYTHERAPY
Brachytherapy 16 (2017) 949–955
Gynecology Oncology

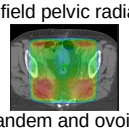
Rectum and bladder spacing in cervical cancer brachytherapy using a novel injectable hydrogel compound

Antonio L. Damato[1], Megan Kassick[2], Akila N. Viswanathan[3,*]
[1]Department of Medical Physics, Memorial Sloan Kettering Cancer Center, New York, NY
[2]Tufts Medical School, Boston, MA
[3]Department of Radiation Oncology and Molecular Radiation Science, Johns Hopkins Medicine, Baltimore, MD

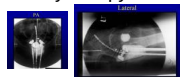


How do these apply to our patient case?

Treated in 2007
3D- 4 field pelvic radiation

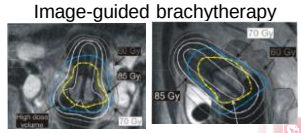


2D- Tandem and ovoid brachytherapy



If treated in 2018…
IMRT pelvic radiation

Image-guided brachytherapy



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.

Stanford MEDICINE

Acute and chronic lower urinary tract dysfunction

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DEPARTMENT OF RADIATION-ONCOLOGY
STANFORD, CALIFORNIA, USA

Workshop # W9, International Continence Society Annual Meeting, Philadelphia
Tuesday, August 28th, 2018

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

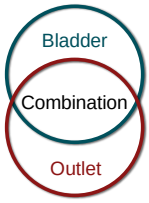
LEARNING OBJECTIVE QUESTIONS:

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

Wein AJ. Classification of neurogenic voiding dysfunction. J Urol. 1981 May;125(5):605–609.

Bladder dose-volume radio-toxicity

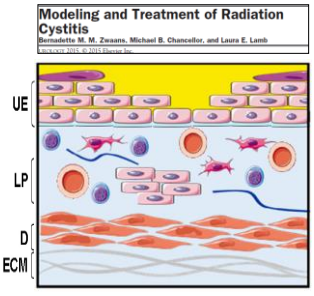
- Bladder only receives partial irradiation during the treatment of gynecologic cancer
  - Lack of knowledge regarding dose-volume bladder radio-toxicity
    - Difficult to assess the amount of bladder wall receiving dose
    - Variation in bladder filling and shape during irradiation
  - Bladder neck 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

Fiorino C, Valdagni R, Rancati T, Sanguineti G. Dose-volume effects for normal tissues in external radiotherapy: pelvis. Radiother Oncol. 2009 Nov;93(2):153–167

Acute inflammatory phase (< 90 days)

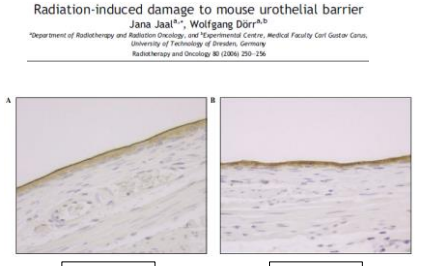
- Loss of GAG layer
- Loss of urothelial cells
- Inflammation
- Edema
- Dilation of blood vessels
- Leaky urothelium
- Stromal cell atypia
- Epithelial hyperplasia

Reversible Inflammation



Zwaans BM, Chancellor MB, Lamb LE. Modeling and Treatment of Radiation Cystitis. Urology. 2015 Nov 10.

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



Control *20 Gy*

Jaal J, Dörr W. Radiation-induced damage to mouse urothelial barrier. Radiother Oncol. 2006 Aug;80(2):250–256

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

Grade	Acute (< 90 days)	%
0	No change	
1	Frequency of urination or nocturia twice pretreatment habit/dysuria, urgency not requiring medication	20-80%
2	Frequency of urination or nocturia that is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anesthetic (e.g., Pyridium)	28+%
3	Frequency with urgency and nocturia hourly or more frequently/dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic/gross hematuria with/without clot passage	
4	Hematuria requiring transfusion/acute bladder obstruction not secondary to clot passage, ulceration, or necrosis	

Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys. 1995 Mar 30;31(5):1341–6.
Kolla SB, Dash PA. Radiation Cystitis: Acute and Chronic. In: Ehrenpreis ED, Marsh R de W, Jr WS, editors. Radiation Therapy for Pelvic Malignancy and its Consequences. Springer New York; 2015. p. 111–8.

Symptoms during the acute phase of radiation

SYMPTOM	UNDERLYING PATHOLOGY
Urinary frequency	Detrusor overactivity
Urinary urgency	Leaky urothelium
Dysuria	Intrinsic sphincter deficiency
Stress urinary incontinence	Poorly compliant bladder
Urgency urinary incontinence	Fistula
Mixed urinary incontinence	Ureteral stricture
Microscopic and gross hematuria	Urethral stricture
	Radiation cystitis

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

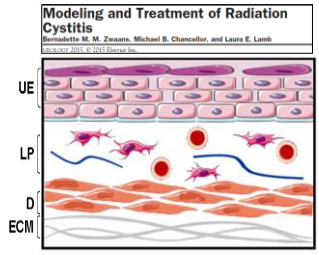
Basic Science Investigational
- Myofibroblast detrusor injections
- Muscle derived progenitor cells
- Intravesical liposomal tacrolimus

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

Zwaans BM, Chancellor MB, Lamb LE. Modeling and Treatment of Radiation Cystitis. Urology. 2015 Nov 10.

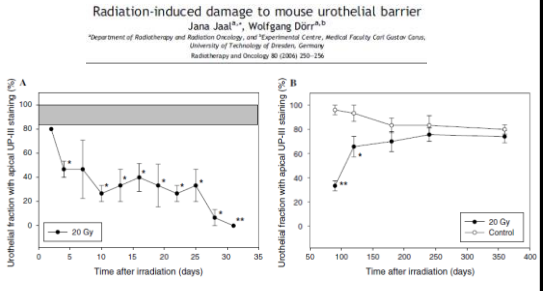
Latent recovery phase (Months-Years)

- Endarteritis
- Urothelial proliferation
- Leaky urothelium ?



Zwaans BM, Chancellor MB, Lamb LE. Modeling and Treatment of Radiation Cystitis. Urology. 2015 Nov 10.

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

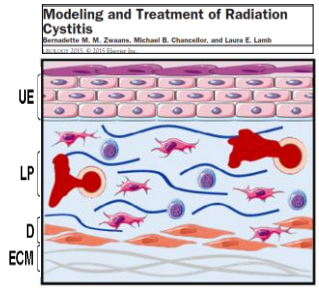


Jaal J, Dörr W. Radiation-induced damage to mouse urothelial barrier. Radiother Oncol. 2006 Aug;80(2):250–256

Late chronic phase (Years-Decades)

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

Fibrosis

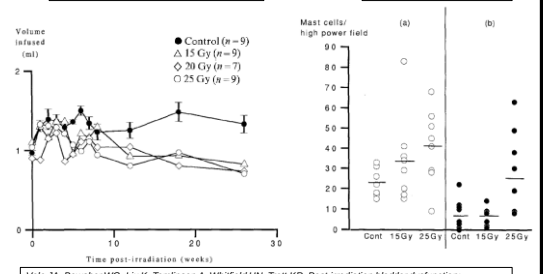


Zwaans BM, Chancellor MB, Lamb LE. Modeling and Treatment of Radiation Cystitis. Urology. 2015 Nov 10.

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

Bladder compliance

Mast cells



Vale JA, Bowsher WG, Liu K, Tomlinson A, Whitfield HN, Trott KR. Post-irradiation bladder dysfunction: development of a rat model. Urol Res. 1993;21(6):383–388

RTOG classification of genitourinary toxicity: Late / Chronic

Grade	Late / Chronic	%
0	None	
1	Slight epithelial atrophy; minor telangiectasia (microscopic hematuria)	
2	Moderate frequency; generalized telangiectasia; intermittent macroscopic hematuria	Minor 45% (5 years)
3	Severe frequency and dysuria; severe telangiectasia (often with petechiae); frequent hematuria; reduction in bladder capacity (< 150 cc)	Major 7.7% (3 years) 9.3% (5 years)
4	Necrosis/Contracted bladder (capacity < 100 cc); severe hemorrhagic cystitis	11.1% (10 years) 13% (15 years) 14.4% (20 years)

Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys. 1995 Mar 30;31(5):1341–6.
Kolla SB, Dash PA. Radiation Cystitis:Acute and Chronic. In: Ehrenpreis ED, Marsh R de W, Jr WS, editors. Radiation Therapy for Pelvic Malignancy and its Consequences. Springer New York; 2015. p. 111–8.

Chronic radiation induced lower urinary tract complications in the female

SYMPTOM	UNDERLYING PATHOLOGY
❑ Urinary frequency	❑ Detrusor overactivity
❑ Urinary urgency	❑ Leaky urothelium
❑ Dysuria	❑ Intrinsic sphincter deficiency
❑ Stress urinary incontinence	❑ Poorly compliant bladder
❑ Urgency urinary incontinence	❑ Fistula
❑ Mixed urinary incontinence	❑ Ureteral stricture
❑ Microscopic and gross hematuria	❑ Urethral stricture
	❑ Radiation cystitis

What are the most common LUT dysfunctions after pelvic radiation?

LUT dysfunction after chemo-radiation (CCRT) versus radical hysterectomy (RH)

Lower urinary tract dysfunction and quality of life in cervical cancer survivors after concurrent chemoradiation versus radical hysterectomy
Chanita Katepratoom · Tarinee Manchana · Napapat Amornwichet
Int Urogynecol J (2014) 25:91–96

❑ Methods
- Retrospective review of cervical cancer survivors (n=70)
- Compare LUT dysfunction between patients who received concurrent chemoradiation (CCRT) versus radical hysterectomy (RH)
  - › 54 Gy pelvic radiation with 2 or 3 high-dose-rate brachytherapy, concurrent with platinum based chemotherapy
  - › Urodynamics performed at least 3 years after treatment

Katepratoom C, Manchana T, Amornwichet N. Lower urinary tract dysfunction and quality of life in cervical cancer survivors after concurrent chemoradiation versus radical hysterectomy. Int Urogynecol J. 2014 Jan;25(1):91–6..

LUT dysfunction after chemo-radiation (CCRT) versus radical hysterectomy (RH)

❑ Urodynamic Results
- Radiation = Storage dysfunction
  - › Poorly compliant bladder
  - › Increased bladder sensation
- Hysterectomy = Voiding dysfunction
  - › High post-void residual urine and void with abdominal straining
  - › Increased capacity
  - › Weakened detrusor

Urodynamic parameters	CCRT (N=35)	RH (N=35)	P value
Uroflowmetry			
Voided volume (ml)	207.2±110.9	284.3±230.3	0.79
Maximum flow rates (ml/s)	17.8±8.9	18.4±8.8	0.78
Postvoid residual urine (ml)	7.7±15.0	47.6±71.9	0.002
Filling cystometry and pressure-flow studies			
MCC (ml)	317±122.9	468±129.3	<0.001
DPMCC (cmH_2O)	10.4±10.5	11.7±12.7	0.63
Compliance (ml/cmH_2O)	54.1±43.3	71.3±51.4	0.13
DPMF (cmH_2O)	38.9±18.4	30.5±13.1	0.03
Urethral pressure profile			
MUCP (cmH_2O)	71.1±29.2	71.8±33.4	0.94
FUL (mm)	18.5±1.9	19.7±4.6	0.24

All values are showed as mean ± standard deviation
MCC maximum cystometric capacity; *DPMCC* detrusor pressure at maximum cystometric capacity; *DPMF* detrusor pressure at maximum flow; *FUL* functional urethral length; *MUCP* maximum urethral closure pressure

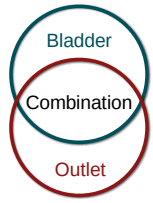
Katepratoom C, Manchana T, Amornwichet N. Lower urinary tract dysfunction and quality of life in cervical cancer survivors after concurrent chemoradiation versus radical hysterectomy. Int Urogynecol J. 2014 Jan;25(1):91–6..

Systematic approach to the radiated bladder and outlet using ICS terminology

❑ Storage symptoms
- Daytime frequency, nocturia, urgency, urinary incontinence, bladder sensation (increased, reduced)

❑ Voiding symptoms
- Slow stream, intermittency, hesitancy, straining
- Incomplete emptying, post micturition dribble

❑ Urinary Incontinence: Involuntary leakage of urine
- Stress: With effort, exertion, sneezing or cough
- Urge: Accompanied / preceded by urgency
- Mixed: Combination of stress and urge
- Continuous (Fistula, devastated outlet, end stage bladder)



Abrams P, et al. The Standardisation of Terminology of Lower Urinary Tract Function: Report from the Standardisation Sub-committee of the International Continence Society, NUU 21: 167-178, 2002
Haylen BT, et al. An IUGA/ICS joint report on the terminology for female pelvic floor dysfunction. Neurourol Urodyn. 2010;29(1):4-20.

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

❑ At discretion – urine culture, bladder diaries, uroflow/PVR

❑ Complicated patient – cystoscopy, renal-bladder ultrasound
- Urodynamics considered when *invasive, potentially morbid or irreversible treatments are considered*.

Gormley EA, et al. Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) In Adults: AUA/SUFU Guideline, 2014
Winters JC, et al. Urodynamic studies in adults: AUA/SUFU guideline. J Urol. 2012 Dec;188(6 Suppl):2464-72.

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 early chronic phase of radiotherapy (RTOG Grade 1-2)

Bladder Dysfunction

Overactive Detrusor

- 1st, 2nd and 3rd line OAB treatments
  - 1st line behavior modification
  - 2nd line pharmacotherapy
  - 3rd line chemodenervation, neuromodulation

Underactive Detrusor

- Intermittent catheterization
- Suprapubic catheter
- Pharmacologic outlet reduction (i.e. tamsulosin)

Outlet Dysfunction

Intrinsic Sphincter Deficiency

- Bulking agents (i.e. Coaptite)
- Biologic bladder neck suspension
- Avoid synthetic sling

Outlet Obstruction

- Urethral stricture dilation
- Urethral stricture ablation/incision

Anticholinergic Treatment (Clinical Trials)

Author	Cohort (N patients)	Follow-Up	Objective Findings	Subjective Findings	Notes
Jaszczynski (2016)	N = 300 (N = 249 women); Single arm observational study solifenacin 5mg daily for post-irradiation bladder	6 months	Improvement in cystometric capacity*, volume at 1st desire*, Pdet@capacity*	Improvement in # micturitions/day*, nocturia*, urgent episodes*, incontinence*	38 month (mean) interval between RT and treatment. Solifenacin well tolerated
Yan (2017)	N = 60 vs. 64; RCT PrCA s/p brachytherapy, trospium 20mg BID + tamsulosin vs. tamsulosin alone	6 months	No difference in Qmax and PVR from baseline	Improvement in IPSS* and QoL* in trospium group. No difference in voiding score.	No women

Jaszczyński J, Kojs Z, Stelmach A, et al. Post-Irradiation Bladder Syndrome After Radiotherapy of Malignant Neoplasm of Small Pelvis Organs: An Observational, Non-Interventional Clinical Study Assessing VESIcare®/Solifenacin Treatment Results. Med Sci Monit. 2016;22:2691-2698.
Yan M, Xue P, Wang K, Gao G, Zhang W, Sun F. Does combination therapy with tamsulosin and trospium chloride improve lower urinary tract symptoms after SEEDS brachytherapy for prostate cancer compared with tamsulosin alone? : A prospective, randomized, controlled trial. *Strahlenther Onkol*. 2017;193(9):714-721. doi:10.1007/s00066-017-1162-5

Bulking agents (Clinical trials)

Author	Cohort (N patients)	Follow-Up	Objective Findings	Subjective Findings	Notes
Plotti (2009)	N = 24 (N = 5 prior RT); Single arm prospective observational study of Macroplastique in women w/ de-novo SUI s/p radical Hx	12 months (minimum)	Frequency of incontinence on the 3-day voiding diary reduced (14.5±5.8 vs 4.3±7.9 episodes per 3 days, p<0.05)	Overall success rate was 84% (10 patients cured and 10 improved)	No intraoperative or postoperative early complications were found. Preoperative urethral hyper-mobility noted in the 4 patients who were not success
Krhut (2016)	N = 46 (N = 24 prior RT); Multi-center single arm prospective observational study of Bulkamid in women w/ severe SUI (w/ vs. w/o prior RT)	12.4 months (mean)	No clinically significant between group changes in urodynamic parameters after Bulkamid (VV, Qmax, PVR, Cap, MUCP)	Complete continence in 25% of patients after RT (vs. 36.4% w/o). Improved urine leakage*, ICIQ-UI* and PPBC* both groups	Mean 93 month (range 16-384) interval between RT and injection

Plotti F, Zullo MA, Sansone M, et al. Post radical hysterectomy urinary incontinence: a prospective study of transurethral bulking agents injection. *Gynecol Oncol*. 2009;112(1):90-94. doi:10.1016/j.ygyno.2008.09.022
Krhut J, Martan A, Jurakova M, Nemec D, Masata J, Zvara P. Treatment of stress urinary incontinence using polyacrylamide hydrogel in women after radiotherapy: 1-year follow-up. *Int Urogynecol J*. 2016;27(2):301-305. doi:10.1007/s00192-015-2834-2

Biologic bladder neck suspension (limited data)

Author	Cohort (N patients)	Follow-Up	Objective Findings	Subjective Findings	Notes
O'Reilly (2002)	N = 121 (N = 1 prior RT); Case series cadaveric fascia lata sling in women w/ SUI	6.5 months (mean); 4-13 months (range)	RT LPP 10 cmH2O preoperative and 21 cmH2O postoperative	8 of 121 women had recurrent SUI	100% of RT patients (N = 1) had recurrent SUI at 12 months
Lowman (2007)	N = 1; Case report, TVT with porcine interposition graft after vulvar cancer RT	3 months	Positive cough stress test at 3 months	80% subjective improvement in symptoms, occasional SUI	19 year interval between RT and surgical intervention

O'Reilly KJ, Govier FE. Intermediate term failure of pubovaginal slings using cadaveric fascia lata: a case series. *J Urol*. 2002;167(3):1356-1358
Lowman J, Moore RD, Miklos JR. Tension-free vaginal tape sling with a porcine interposition graft in an irradiated patient with a past history of a urethrovaginal fistula and urethral mesh erosion: a case report. *J Reprod Med*. 2007;52(6):560-562

Bladder and outlet treatments during the end-stage chronic phase of radiotherapy (RTOG Grade 3-4)

Hemorrhagic Cystitis

- Electrocautery ablation
- Laser ablation
- Intravesical instillations
- Hyperbaric oxygen
- Cystectomy

Fistula

- Ureter – reimplant versus urinary diversion
- Vesico-vaginal – urinary diversion
- Enterovesical – bowel diversion

Small Fibrotic Bladder

- Bladder augment
- Indwelling suprapubic tube
- Continent vs. Incontinent Urinary diversion +/- cystectomy

Devastated Bladder Outlet

- Tight biologic bladder neck sling
- Outlet closure procedure and suprapubic tube
- Avoid artificial urinary sphincter

Radiation changes are often progressive/irreversible
-
Patient expectations must be aligned with likely outcome

Artificial Urinary Sphincter – High erosion in women

Author	Cohort (N patients)	Follow-Up	Objective Findings	Subjective Findings	Notes
Mundy (1989)	N = 30 (N = 9 prior RT); Case series total urethral substitution (N = 4 treated with AUS)	NR	50% sphincter weakness incontinence with AUS	2 of 4 patients (colonic substitution and AUS) failed and required diversion "not satisfactory"	All post-RT had hysterectomy. Interval between RT and surgery NR.
Duncan (1992)	N = 29 (N = 7 prior RT); Case series AUS in women	NR	NR	4 of 12 patients had "satisfactory result" (N = 7 prior RT)	8 of 12 patients cuff erosion (N = 7 prior RT).
Vayleux (2011)	N = 215 (N = 9 prior RT); Case series AUS in women	6 years (mean)	Overall 73.5% continent (0-1 pad per day). Failure (Incontinence after AUS in 23.7%)	Overall 79% satisfied	Pelvic radiotherapy (Continence failure OR 4.37, CI 1.02-18.5). Erosion in 3 of 9 RT patients

Mundy AR. Urethral substitution in women. *Br J Urol*. 1989;63(1):80-83
Duncan HJ, Nurse DE, Mundy AR. Role of the artificial urinary sphincter in the treatment of stress incontinence in women. *Br J Urol*. 1992;69(2):141-143
Vayleux B, Rigaud J, Luycks F, et al. Female urinary incontinence and artificial urinary sphincter: study of efficacy and risk factors for failure and complications. *Eur Urol*. 2011;59(6):1048-1053. doi:10.1016/j.eururo.2011.03.006

Continent vs. Incontinent Urinary diversion +/- cystectomy

Author	Cohort (N patients)	Follow-Up	Objective Findings	Subjective Findings	Notes
Wilkin (2005)	N = 26 (N = 12 prior RT); series Indiana pouch at time of exent. for recurrent gyn. cancer	12 months (minimum); 48.5 months (mean, prior RT group)	3 of 12 patients pouch incontinence efferent limb	83% of RT patients had one or more complications	32 month (mean) interval between RT and surgery
Al Hussein Al Awamlh (2015)	N = 29; Case series cystectomy and diversion after pelvic RT (N = 5 women)	37.3 months (median)	NR	65.5% 30-day postoperative complications	87 month (median) interval between RT and 1st symptoms
Banerji (2015)	N = 28; Case series ileal conduit after cervical cancer RT (N = 18 vesico-vaginostomy)	13.2 months (mean)	NR	Global Impression of Change Scale 5.2/7 (vs. 3/7 w/o conduit, p = 0.06)	9.8 year (mean) interval between RT and cystitis

Wilkin M, Horwitz G, Seetharam A, et al. Long-term complications associated with the Indiana pouch urinary diversion in patients with recurrent gynecologic cancers after high-dose radiation. *Urol Oncol*. 2005;23(1):12-15.
Al Hussein Al Awamlh B, et al. Assessment of the QOL and outcomes in patients undergoing cystectomy and urinary diversion for the management of radiation-induced refractory disease. *Urology*. 2015;85(2):394-400.
Banerji JS, et al. Early urinary diversion with ileal conduit and vesicovaginostomy in the treatment of radiation cystitis due to carcinoma cervix: South India. *ANZ J Surg*. 2015;85(10):770-773

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.

- Urodynamic finding: Intrinsic sphincter deficiency (VLPP 40 cm H2O), detrusor overactivity, Pdet@Qmax 8 cm H2O, PVR 0 mL
- Treatment: Mesh excision, bulking agent, 2nd vs. 3rd line OAB treatment, if refractory then biologic sling +/- suprapubic tube

Mesh exposure
Bladder outlet insufficiency
Detrusor overactivity

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.

ICS 2018 PHILADELPHIA

DISCUSSION

Stanford MEDICINE

Radiation induced vaginal dysfunction

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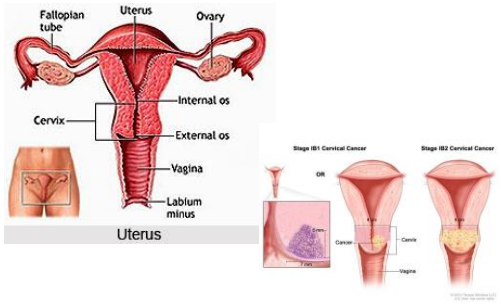
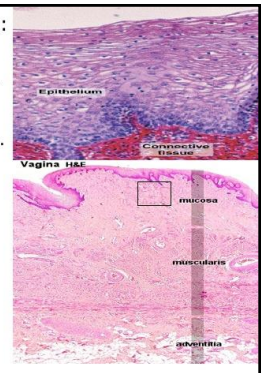
Workshop # W9, International Continence Society Annual Meeting, Philadelphia
Tuesday, August 28th, 2018

Gynecologic malignancies and targeted treatment locations



Vagina consist of three layers :

- Mucosa
  - Strat. Sq. Nonkeratinized Epit. (>> glycogen)
  - Lamina propria : loose fibroelastic C.T. , rich vascular.
  - **No glands** ; vaginal fluid comes from transudation & cervical glands
- Muscularis
  - Smooth muscle, inner circular & outer longitudinal
- Adventitia
  - Dense fibroelastic C.T



Relationship between exposure to XRT and PFDs in endometrial cancer survivors

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

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
- ❑Lost of vaginal elasticity and stenosis due to fibrosis
- ❑Loss of ovarian function resulting in decreased lubrication
- ❑Late toxicity – 18-32% of patients

Rodrigues A et al. Impact of pelvic radiotherapy on female sexuality. Arch Gynecol Obstet 2012;285:505-14

- ❑ Sexual function - addressed in ICS 2015 Roundtable presentation – Dr. Shauna Correia, Pelvic floor dysfunction in cancer survivors after radial pelvic surgery and radiation therapy https://www.ics.org/tv?play=3237

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

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

Abitbol MM, Davenport JH. Obstet Gynecol 1974 Aug;44(2):249-56

Treatment characteristics of survivors with and without loss of vaginal elasticity

[Treatment characteristics of survivors with and without 'absence of vaginal elasticity'.

	Survivors with the symptom N = 24 n/N (%)	Survivors without the symptom N = 54 n/N (%)	p-Value
Surgery	18/24 (75)	51/54 (94)	0.020
TAH ± SOE ± omentectomy	14/24 (58)	43/54 (80)	
TAH ± SOE ± omentectomy ± lymph node sampling	1/24 (4)	1/54 (2)	
Radical hysterectomy + pelvic lymphadenectomy	1/24 (4)	5/54 (9)	
Vulvar resection ± lymph node resection	2/24 (8)	2/54 (4)	
Chemotherapy	14/24 (58)	30/54 (55)	0.17
Before and or after EBRT	12/24 (50)	30/54 (56)	
Concomitant with EBRT	2/24 (8)	0/54 (0)	
EBRT doses (Gy) delivered to the target			
Mean dose Gy, (SD)	50.7 (11.7)	42.6 (8.5)	0.0085
Median dose Gy, (range)	48.8 (39.6–70.0)	48.0 (10.8–67.0)	
Field technique			1.0
Two opposing fields	11/24 (46)	26/54 (48)	
Four-field box	13/24 (54)	28/54 (52)	
Target area			0.18
Pelvic field	14/24 (58)	21/54 (39)	
Abdominal field	8/24 (33)	28/54 (52)	
Pelvic field + paraaortic lymph nodes	0/24 (0)	3/54 (6)	
Pelvic or vulvar field + inguinal lymph nodes	2/24 (8)	2/54 (4)	
Mean time since EBRT, months (SD)	96.5 (46.5)	87.7 (35.5)	0.61

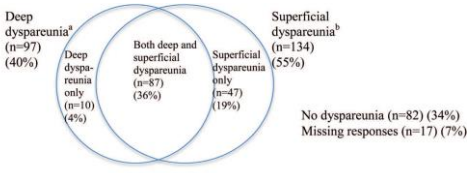
Abbreviations: TAH, Total Abdominal Hysterectomy; SOE, Salpingo-oophorectomy.

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

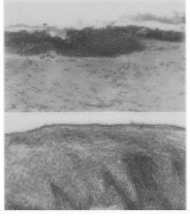


[a] Deep dyspareunia includes women reporting deep dyspareunia only and deep dyspareunia in combination with superficial dyspareunia.
[b] Superficial dyspareunia includes women reporting superficial dyspareunia only and superficial dyspareunia in combination with deep dyspareunia.

Kollberg KS et al. Acta Oncologica, 2015;54:772-779

Cellular changes in the vaginal in response to estrogen and radiotherapy

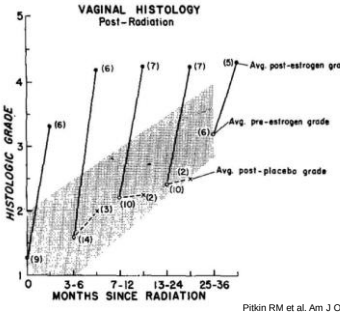
- ❑Acute radiation vaginitis is managed with topical intravaginal estrogens
- ❑Irradiation has an inhibitory effect on cellular division with resulting reduction in thickness of epithelium
- ❑Estrogen increases mitosis and proliferation of vaginal basal cells



Less in patients immediately post radiation that in those >3 months after radiation

Pitkin RM et al. Am J Obstet Gynecol. 1965 May 15;92:175-82

Vaginal histology grade changes with estrogen use after radiation therapy



Pitkin RM et al. Am J Obstet Gynecol. 1965 May 15;92:175-82

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)

Greenberg H et al. Gynecol Oncol 1984 Mar;17(3):301-7

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)

Many options available, including:

- Replens
- KY Liquibeads
- Hyalo Gyn
- HyaloFemme
- Key-E
- Crème de la Femme
- Emerita
- Luvena

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, Sliquid

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:

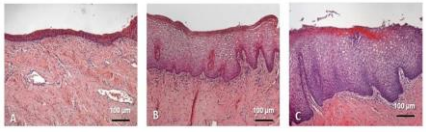
- Coconut, avocado, corn, olive, peanut,
- Non-irritating
- Should not be used with latex items

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

Biglia N, et al. Low-dose vaginal estrogens or vaginal moisturizer in breast cancer survivors with urogenital atrophy: a preliminary study. Gynecol Endocrin 2010;26(6)

Vaginal lubrication - laser vaginal therapy



Histological preparation of vaginal mucosa sections stained with haematoxylin and eosin (H&E). **(A)** Vaginal mucosa in the basal condition with a thinner epithelium typical of atrophic vaginitis. **(B)** The same patient one month after the 1st ***MonaLisa Touch®*** session. It is evident the thicker epithelium of the mucosa. **(C)** The same patient one month after the 2nd ***MonaLisa Touch®*** session. It is possible to observe a further thickening of the mucosa epithelium.

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

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.

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
  - 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)

Radiation and surgery for pelvic floor disorders

- Patients with previous irradiation are at high risk for complications following pelvic reconstructive surgery. Increased risk of erosions with mesh implants (case report of TVT sling erosion post XRT, Lowman J etal. J Repro Med 2007 Jun;52(6):560-2
- 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

Physiotherapy of the radiated pelvic floor

Stephanie Bernard, PhD(c), PT

Université Laval, Québec, Canada

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

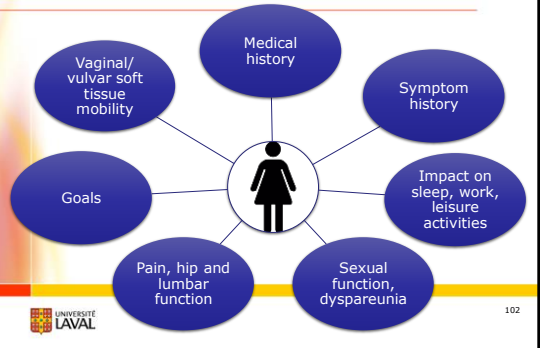
Case presentation – Ms. J

- 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;

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



Assessment of the pelvic floor muscles (PFMs)

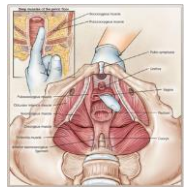
PFM assessment

- 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



Assessment of the pelvic floor muscles (PFMs)

- **PFM clinical assessment of contractility**
  - Digital
  - Ultrasound[16]

Vaginal ultrasound (click video to play)

Assessment of the PFMs

How is contractility impaired after irradiation?

REVIEW

Effects of radiation therapy on the structure and function of the pelvic floor muscles of patients with cancer in the pelvic area: a systematic review

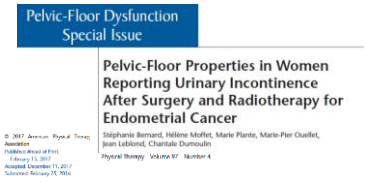
Assessment of the PFMs

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?



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?

Assessment of the PFMs

How is muscle tone/anatomical structure impaired after irradiation?

- Systematic review : No change in anal sphincter thickness on anal ultrasound[4]

Assessment of the PFMs

How is muscle tone/structure impaired after irradiation?

- Cross-sectional study: ↓ antero-posterior opening at vaginal entry[7]
- 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

©BandhaYoga

1. Exercises for the irradiated PFM

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.)

©StephanieBernard

1. Exercises: do they work?

- Pelvic floor muscle training improved strength[15] and UI[9] in gynecological cancer survivors
- Women have a positive attitude towards pelvic floor muscle training for UI after gynecological cancer[10]

©Healthy Eating Hub

2. Manual and dilation therapy

Main goals for dilation therapy:

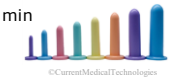
- Prevent vaginal adhesions and stenosis
- Facilitate sexual intercourse
- Facilitate medical assessment of the vaginal canal
- Improve PFM passive mobility and function
- Reduce UI?

©PelvicRelief

2. Manual and dilation therapy

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



©CurrentMedicalTechnologies

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 recommanded lubricant
- 3 times a week during 1st year
- Up to 2 years after RT

Precautions:[11,12]

- 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

3. Bladder training

- Bladder diary
- Education on water and other beverage consumption
- Prevention of constipation
- Urge-control strategies (PFMT)
- Bladder emptying techniques
- Mindfulness/body awareness meditation

3. Bladder training

- 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

Case presentation

Month 2:

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

Case presentation

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.

Thank you!

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DISCUSSION