

Radiation cystitis and

side effects of instillation therapy

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Bladder - an innocent victim

- Pelvic radiation external and brachytherapy
- Instillation therapy BCG and mutamycin
- Systemic chemotherapy cyclofosfamide



Presentation Diagnostics Treatment



Pelvic radiation syndrome

- LUTS frecvency, urge, capasity
- Strictures
- Incontinence
- Hemoragic cystitis
- Fistulas
- Bowel problems
 - Proctitis and enteritis
- Vaginal problems

Impact on Quality of Life



Radiation cystitis

 $\mathbf{\mathbf{A}} \mathbf{\mathbf{\Psi}} \mathbf{\mathbf{\Theta}}$

- In 5% of patients after pelvic radiotherapy
- Acute cystitis 3-6 months
- Late cystitis after 6 months

- Balanced clinical descisions
 - Based on risks and benefits













Late Radiation cystitis

- Dysuri
- Frequency
- Urgency
- Bladder pain
- Hematuria
- Hematuria
- Urosepsis
- Bladder rupture
- Renal failure
- Important to exclude other causes of hematuria





Bothersome problems

Life treatening





RTOG	Long-term complications and toxicity after radiation therapy
Grade 1	Frequency Dysuria Urgency not requiring medication
Grade 2	Moderate urinary frequency (<1/h)) Occasional hematuria Numerous telangiectasias
Grade 3	Severe urinary frequency (>1/h) Severe dysuria Frequent hematuria Bladder capacity < 150 ml
Grad e4	Perforations Fistulas Severe hemorhagic cystitis Bladder capacity < 100 ml
Grade 5	Any fatal complication

Radiation in general UNIVERSITY OF BERGEN



- Immediate Cell Death
- Free Oxygen radicals RADIOLYSIS lipid perioxidation cell membranes
- Late Cell Death
- DNA changes
 - Genetic changes

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- Alter replication









Pelvic Radiation

- Radiation site field
- Volume of exposed tissue
- Treatment schedule
 - Total dose, dose per fraction, type of radiation
- Concomitant chemotherapy
- Predisposing
 - Tobacco use, vascular disease, inflammatory bowels, diabetes and hypertension

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Bloodvessels







- Subendothelial proliferation
- Edema
- Thickening of Media
- Obstruction of vessels and scaring
 - Hypoxia and necrosis
 - Collagen changes



- Changes also affect the muculature
- Neuromuscular interplay
- Perivascular fibrosis





3 different phases







Diagnostics of radiation cystitis

Patients history

Findings at Cystoscopy

• telangiectasy- epitelial atrophy – ulcer- strictures

Volumetric analysis

- Reduced bladder capacity?
- Residual urine Urinary Leakage Flow

Hematuri with relatively normal bladder wall- CT urography



Treatment of radiation cystitis

- 1. First line hematuria treatment
- 2. Anticholinergic, betaagonists,
- 3. GAG replenisment therapy
- 4. Formalin
- 5. Aluminium
- 6. Ablative therapy
- 7. Arterial embolisation
- 8. HyperBaricOxygen therapy
- 9. Cystectomy PAGE 14





First line treatment SITY OF BERGEN

- Hyper-hydration
- Bladder irrigation
 - Coupious bladder wash outs
- Reversal of anticoagulation
- Transurethral surgery
 - Electrocoagulation
 - Laser
- Bloodtransfusion





First line treatment

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First line treatment

- Hyper-hydration
- Bladder irrigation

 Coupious bladder wash outs
- Reversal of anticoagulation
- Transurethral surgery
 - Fulguration
 - Laser
- Bloodtransfusion







GAG replenisment therapy of Bergen



- Reduce epithelial cells exposure to host urine
- Hyalorunic acid / Chondroitin sulphat/Sodium pentosan sulphat
- Different solutions available today
 - Uracyst, cystistat and ialuril
- Symptoms Improve





Intravesical Formalin



- Precipitating cellular proteins within the epithelial layer
- Occlusion and fixation of the teleangiectatic and friable vasculature
- Concentrations/formula **1%**, 2%, 4% (10%)
- Complete Response: 37.5%- 88%
- Complications
 - hydronephrosis, VUR, Vesicovaginal fistula, ureteral stenosis, death





Intravesical Formalin- procedure

- General anesthesia
- Cystoscopy, clot evacuation , fulguration
- Cystogram to ensure no vesicouretral reflux
- Protect exteranl genitalia
 - Wrapping -petroleum jelly
- Indwelling catheter balloon with slight tension
- 15 cm pressure in 10-15 minutes
- Irrigation with sterile water first
- Continous irrigation with normal saline





Intravesical Formalin- procedure

- Complicated to perform in a safe manner
- Few cases low experience
- As a last solution when everything else does not work

At our hospital it is now taken out of our repertoare - And changed to intravesical alum



Intravesical Aluminium sergent



- Stimulate vasoconstriction, decrease capillary permeability, precipitate proteins at cell surface
- Not as effective as formalin but improved side effect profile
- Bladder spasm could be treated with anticholinergic
- Systemic absorption could cause neurotoxicity
- Concentration :1% (potassium or ammonium alum sulphate)
- Complete response: up to 60 %
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Ablative therapy

- Yag-laser
- Green light laser
- Argon-beam fulguration



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Radiological intervention

- Arterial embolisation
- Limited evidence- small series
- Complete resolution in 92 100 %
- Ischemic complications occurs in 10-62%
 - Skin or bladder necrosis
 - gluteal paresis
 - Brown Sequard syndrome
 - perineal and buttock pain







Hyperbaric oxygen treatment







- 100% oksygen in 90 min 14m «below sea level
- 5 times/week 6-8 weeks



Angiogenesis Stem cell mobilization Reduce inflammation





Hyperbaric oxygen treatment

- RICH-ART study
- Randomized controlled trial in Nordic countries
- Late radiation cystitis
- Treatment was well tolerated and safe
- Improved Quality of Life
- Improved cystoscopic findings
- Less bladder symptoms





Health Related Quality of Life

SF-36 domain	A (HBO, 41)	B (controls, 38)	p-value ¹
Physical functioning	+4.6 *	-1.6	0,08
Role limitations due to physical health	+12.2	-2.1	0,15
Role limitations due to emotional problems	-5.13	-3.8	0,90
Energy/fatigue	+7.2 *	+1.1	0,13
Emotional well-being	+3.8	+0.6	0,41
Social functioning	+5.5	-0.3	0,32
Pain	+8.3 *	+7.1	0,85
General health	+9.3 *	-3.9	<0,001
	¹ p for difference	between groups (cha	nge visit 1to visit







Definitive surgical treatment

• Urinary diversion







The EPIC* questionnaire

Final score 0 (worst) -100 (best)

<80 for inclusion

	More than once a day	About once a day	More than once a week	About once a week	Rarely or never
1. How often have you leaked urine?	0	0	0	0	0
2. How often have you urinated blood?	0	0	0	0	0
3. How often have you had pain or burning with urination?	0	0	0	0	0
 4. Which of the following best describes your urinary control? 5. How many pads or adult diapers 	 No urinary Frequent dr Occasional Total control None 	control whatsoev ibbling dribbling ol	er *		
per day do you usually use to control leakage?	 1 pad per d 2 pads per d 	ay day			
per day do you usually use to control leakage?	 1 pad per d 2 pads per d 3 or more p 	ay day pads per day			
per day do you usually use to control leakage?	 1 pad per d 2 pads per d 3 or more p No problem 	ay day oads per day Very small problem	Small problem	Moderate problem	Big problem
per day do you usually use to control leakage? a. Dripping or leaking urine	 1 pad per d 2 pads per d 3 or more p No problem 	ay day oads per day Very small problem	Small problem	Moderate problem	Big problem
per day do you usually use to control leakage? a. Dripping or leaking urine b. Pain or burning on urination	 1 pad per d 2 pads per d 3 or more p No problem 0 	ay day ads per day Very small problem	Small problem	Moderate problem	Big problem
a. Dripping or leaking urine b. Pain or burning on urination c. Bleeding with urination	 1 pad per d 2 pads per d 3 or more p No problem 0 0 0 	ay day bads per day Very small problem O	Small problem	Moderate problem O	Big problem O O
a. Dripping or leaking urine b. Pain or burning on urination c. Bleeding with urination d. Weak urine stream	 1 pad per d 2 pads per d 3 or more p No problem 0 0 0 0 0 0 0 	ay day bads per day Very small problem 0 0	Small problem O O O O O O O O O O O O O O O O O O O	Moderate problem O O O	Big problem O O O O
a. Dripping or leaking urine b. Pain or burning on urination c. Bleeding with urination d. Weak urine stream e. Waking up to urinate	 1 pad per d 2 pads per d 3 or more p No problem 0 0 0 0 0 0 0 0 	ay day bads per day Very small problem 0 0 0	Small problem O O O O O O O O O O O O O O O O O O O	Moderate problem O O O O O O	Big problem O O O O O O O O
 a. Dripping or leaking urine b. Pain or burning on urination c. Bleeding with urination d. Weak urine stream e. Waking up to urinate f. Need to urinate frequently during the day 	 1 pad per d 2 pads per d 3 or more p No problem 0 <l< th=""><th>ay day ads per day Very small problem 0 0 0 0 0 0 0 0 0</th><th>Small problem Small problem O O O O O O O O O O O O O</th><th>Moderate problem O O O O O O</th><th>Big problem O O O O O O O O O O O O O</th></l<>	ay day ads per day Very small problem 0 0 0 0 0 0 0 0 0	Small problem Small problem O O O O O O O O O O O O O	Moderate problem O O O O O O	Big problem O O O O O O O O O O O O O

7. Overall, how big a problem has your urinary function been for you during the last 4 weeks?

- O No problem
- Very small problem
- Small problem
- Moderate problem
- Big problem

*Wei JT et al., Urology 2000



RTOG Late Radiation Morbidity Scoring Schema

	0	1	2	3	4
BLADDER	None	Slight epithelial atrophy Minor telangiectasia Microscopic hematuria	<i>Moderate frequency</i> Generalized telangiectasia Intermittent macroscopic hematuria	Severe frequency and dysuria Severe generalized telangiectasia Frequent hematuria Bladder capacity (<150 cc)	Necrosis/ Contracted bladder Bladder capacity <100 cc Severe hemorrhagic cystitis



Current management of radiation cystitis: a review and practical guide to clinical management



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Current management of radiation cystitis: a review and practical guide to clinical management



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l	nstillation therapyersity of	Risk category	Definition	Treatment
•	BCG	Low	Primary, singel, TaG1, no CIS, <3 cm	One immediate chemotherapy
•	Indications	Intermediate	In between Frequent recurrence, > 3 cm, G2	BCG or mutamycin one year
•	Side-effects cystitis 80 % hematuri 20 %, LUTS in 70 % in maintenance 	High	T1 G3 CIS Multipple, recurrent and	BCG (2-3 yrs) except for high- high risk who should have
•	Contra: – The 2 first weeks after TURB – Visible hematuria – Traumatic catheterisation – Symptomatic urinary tract infection		>3 cm TaG1, G2, G3 Figure 1: St CIS, Ta ar non-muscle CIS Ta	CVStectomy ages of Bladder Cancer d T1 are classified as invasive bladder cancer T1
•	Be aware – Immuno compromised patients – Lack of BCG?			T2 T3
	Boehm et al 2017 PAGE 33			

How does BCG work?

Immunotherapy

Discovered in 1921 but first uses by Morales in 1972 for bladder cancer

Delayed hypersensitivity reaction Poorly differnetiated cell lines internalise BCG and are sensitive to it

Irritative bladder symptoms –frequency, dysuria and low grade fever usual after second or third instillation and lasts for 1-2 days

- Immune stimulation and Cytokine production

Absorption can cause serious reactions



BCG side-effects

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Symptoms	Management option
Cystitis	NSAID – urine culture – antibiotics – quinolones – anti-TUB and steroids – cystectomy if no response and/or contracted bladder
Hematuria	Urinculture, antibiotics - cystoscopy
Granulomatous prostatis	Quinolones – stop BCG- isoniacid and rifampicin(anti-TUB) 3 months
Epidydimoorchitis	Quinolones- stop BCG – orchidectomy may be needed?
Malaise, fever	Usually resolve within 48 hours withor without antipyretics
Arthralgi/arthritis	Rare, considered an automimmune reaction – NSAID - (steroid/ quinolones/anti- TUB)
Persistent fever	Stop BCG permanently- antimicrobial treatment
BCG sepsis	Prevention- quinolones/anti-TUB 6 months – high dose steroids – antibiotics
Allergic reaction PAGE	Antihistamines and anti inflammatory agents –delay therapy- may be high dose quinolones/anti-TUB

Instillation therapy for bladder cancers

Chemotherapy – Mutamycin, epirubicin

- When one shot after TUR-B in low risk
- Effect reduce recurrence
- Duration may also be used in case of BCG intolerance
- Side-effects
 - Less LUTS problem than BCG



Bladder problems after systemic chemotherapy

Δffe	ct the GAG laver- permeability			Cyclophosphamide
	or the OAO layer permeasing			Idarubicin
—	Thrive an Inflammatory and hypersens	itivity response		Ifosfamide
				Paclitaxel/carboplatin therapy
			Intravesical chemotherapy	Doxorubicin
Сус	lophoshamide (CP)			Epirubicin
_	Hematopoietic stem cell transplantation	n		Mitomycin C
			Other therapeutic agents and environmental toxins	BCG
—	B cell malignancy			Gentian violet
_	Immunoinflammatory conditions as We	egeners granulomatosis systemi		Ketamine hydrochloride
	lupus on the motorus and roumstaid or	thritic		Tiaprofenic acid
	iupus erytnematosus and reumatoid ar	unnus		Topical agents
			RT	Including brachytherapy
_	Acrolein, urinary metabolite of CP and i	fosfamide(IF)		
	develop weeks and months after CP			
		Grading of HC as defined by Droller et al. [9]		
	IF give worse symptoms			

Grade	Symptoms
I	Non-visible haematuria
п	Macroscopic haematuria
III	Macroscopic haematuria with small clots
IV	Gross haematuria with clots causing urinary tract obstruction requiring instrumentation for clot evacuation

Frequently reported causes of chemical- and RT-induced HC

Busulfan

Chemotherapeutic agents

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Treatment

- Pretreatment with Mesna
- Hyperhydration, bladder irrigation
- GAG replenisment therapy
- HBO
- Estrogen, prostaglandines
- (Formalin and aluminium)

The oncologist usually treat these patients at their own department sucessfully





Conclusion

Side effects from Succesfull oncologial treatment

Impact on Quality of life

Balance your clinical decisions on risks and benefits



Pasient 1 blødninger i 2013, elektrokoagulasjon i mars 2014





Pasient 2 strålebehandling høst 2011, turp forut og etterpå





Pasient 2



Pasient 3 Ralp 2007, strålet for psa residiv, hematuri siden april, cystistat



Pasient 4 prostatektomi 2007, strålet 2010, mye vannlatningsplager og senere hematuri