Associazione Italiana
Radioterapia Oncologica
Gruppo Interregionale
Lazio/Abruzzo/Molise

Le terapie di supporto in Radioterapia:

Verso una Guida Pratica

Lunedì 4 Dicembre 2017
Centro Studi Cardello
Via del Cardello 24 – Roma

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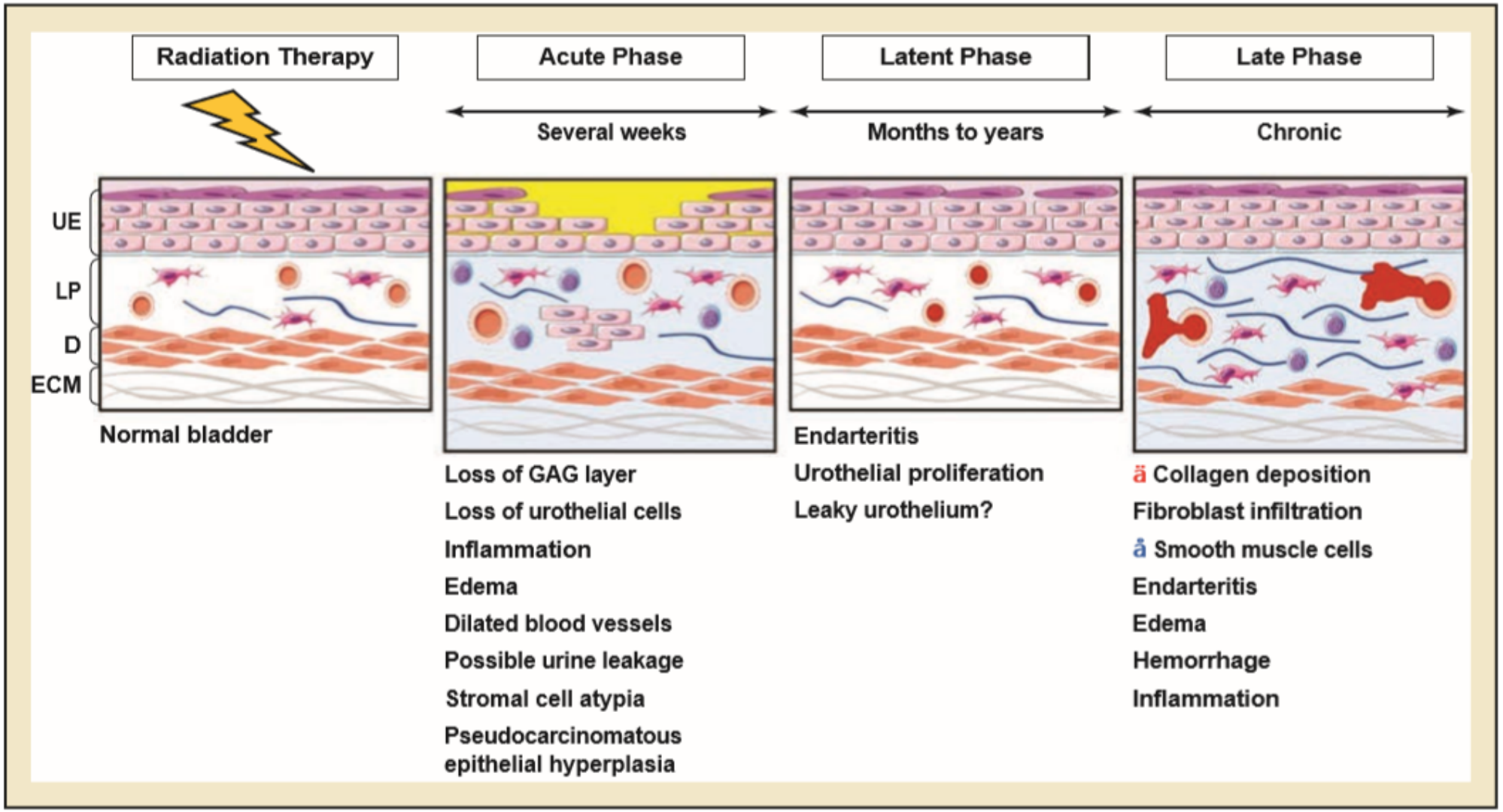
Divisione di Radioterapia
Ospedale Regionale San Salvatore L'Aquila

Natural history of radiation –related cystitis



Clinical Definition of Radiation cystitis

Storage Symptoms	Voiding Symptoms	Post-Micturition Symptoms
▪ Urgency ▪ Frequency (≥8 micturitions/24 hrs) ▪ Incontinence ▪ Nocturia (Waking up ≥ 2 times at night to void)	▪ Poor flow ▪ Intermittency ▪ Straining ▪ Hesitancy ▪ Terminal dribble	▪ Post-void dribble ▪ Incomplete emptying

Suggestive of Radiation cystitis

Suggestive of radioinduced Bladder Outlet Obstruction

LUTS – Low Urinary Tract Symptoms

+

Microscopic +/- Macroscopic Haematuria

Haemorrhagic Cystitis

Medical treatments

Conservative treatment of Radiation induced cystitis:

1. Topical Therapy
2. Oral Therapy
3. Parental Therapy

Medical treatments

Conservative treatment of Radiation induced cystitis:

1. Preventive Treatment

2. Symptomatically approach

Medical treatment for non haemorrhagic Radiation induced cystitis

Alpha1-adrenoceptor antagonists

Glycosaminoglycan Replacement with Chondroitin Sulphate

Hyaluronate and chondroitin sulfate

Chondroitin sulfate

Botulinum toxin A injection

Solifenacin

Vitamin E and pentoxifylline

Medical treatment for radiation-induced haemorrhagic cystitis

Intravesical hyaluronic acid instillation

Hyperbaric oxygen

WF10

Formalin

Non-haemorragic radiation cystitis

Antimuscarinic drugs

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MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

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Post-Irradiation Bladder Syndrome After Radiotherapy of Malignant Neoplasm of Small Pelvis Organs: An Observational, Non-Interventional Clinical Study Assessing VESIcare®/Solifenacin Treatment Results

In favor of use

LE: 2++ GR: B

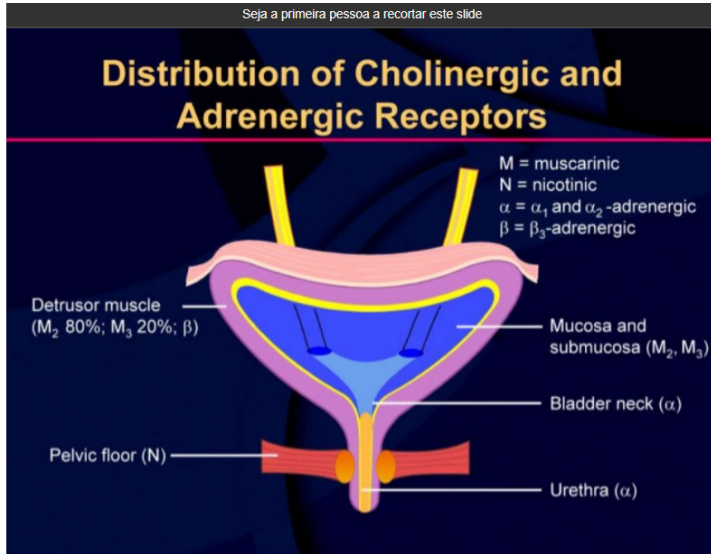

Table 1. Study group – demographic data.

Gender	Number	Gynecological cancer patients	Bladder cancer patients	Rectum cancer patients	Prostate cancer patients
Women	249	230	17	2	–
Men	22	–	10	4	8
Total	271	230	27	6	8

Table 2. Average number of episodes a day.

Feature	Visit I	Visit II	Visit III	Percentage reduction of feature, p
Number of micturition a day	11	10	7	–36%, p<0.01
Including nocturia	4	3	2	–50%, p<0.01
Number of urgent episodes	17	15	8	–53%, p<0.03
Incontinence episodes	7	5	4	–43%, p<0.01

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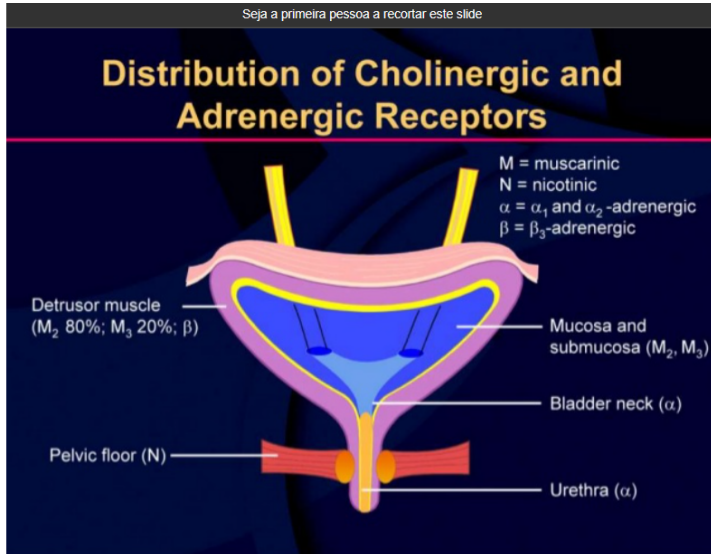


Table 4. How would you describe your present condition?

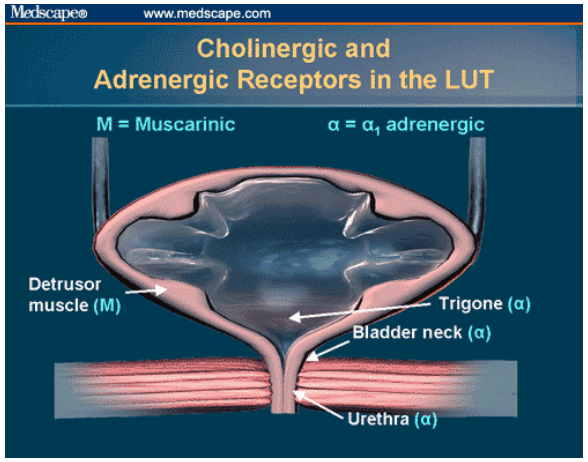
Feature	Visit I	Visit II	Visit III
Very good	6% (16 p.)	6% (16 p.)	8% (22 p.)
Good	10% (27 p.)	17% (47 p.)	22% (60 p.)
Average	62% (168 p.)	72% (195 p.)	66% (179 p.)
Bad	15% (41 p.)	3% (8 p.)	2% (5 p.)
Very bad	7% (19 p.)	2% (5 p.)	2% (5 p.)

Table 5. How, in your opinion, problems with bladder affect your life quality?

Feature	Visit I	Visit II	Visit III
Not at all	2% (5 p.)	8% (22 p.)	10% (27 p.)
A little	10% (27 p.)	29% (78 p.)	35% (95 p.)
Average	35% (95 p.)	49% (133 p.)	45% (122 p.)
Very	53% (144 p.)	14% (38 p.)	10% (27 p.)

Non-haemorragic radiation cystitis

Alpha1 adrenoceptor drugs



Tanaka et al. Radiation Oncology (2014) 9:302
DOI 10.1186/s13014-014-0302-7

RADIATION ONCOLOGY

RESEARCH Open Access

Use of alpha-1 adrenoceptor antagonists in patients who underwent low-dose-rate brachytherapy for prostate cancer - a randomized controlled trial of silodosin versus naftopidil -

Nobumichi Tanaka[1*], Kazumasa Torimoto[1], Isao Asakawa[2], Makito Miyake[1], Satoshi Anai[1], Akihide Hirayama[4], Masatoshi Hasegawa[2], Noboru Konishi[3] and Kiyohide Fujimoto[1]

In favor of use

LE: 1+ GR: B

Table 3 The serial change in mean value (SD) of IPSS and OABSS

Variable	Baseline	1 month	3 months	6 months	12 months
IPSS (total)					
Naftopidil (n=70)	6.8 (4.3)	15.5** (8.0)	17.4** (8.5)	13.5** (7.9)	9.8** (7.1)
Silodosin (n=71)	7.9 (5.5)	15.5** (9.5)	18.3** (9.1)	14.4** (7.9)	9.8** (7.2)
Total (n=141)	7.4 (5.0)	15.5** (8.7)	17.8** (8.8)	13.9** (7.9)	9.8** (7.1)
OABSS (total)					
Naftopidil (n=70)	3.5 (2.2)	6.1** (3.4)	6.8** (3.8)	5.8** (3.2)	4.5** (3.0)
Silodosin (n=71)	3.4 (2.6)	6.2** (3.7)	6.4** (3.5)	5.2** (3.2)	4.0** (3.0)
Total (n=141)	3.4 (2.4)	6.2** (3.6)	6.6** (3.6)	5.5** (3.2)	4.3** (3.0)

Baseline vs. *$p < 0.05$, **$p < 0.01$.

Table 5 The serial change in mean value (SD) of frequency volume chart

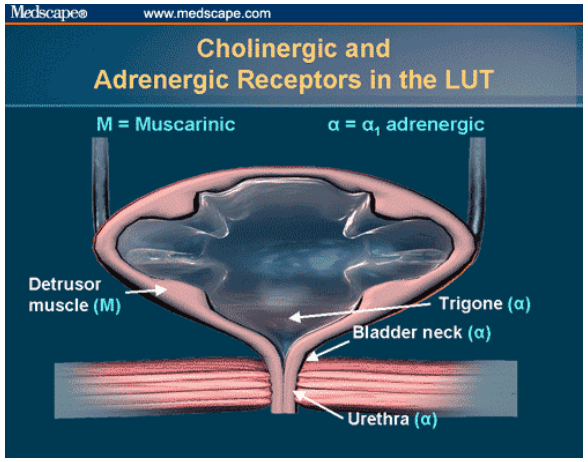
Variable	Baseline	1 month	3 months	6 months	12 months
Total volume (mL/day)					
Naftopidil (n=70)	1915 (756)	1871 (745)	1782** (533)	1718** (652)	1687** (562)
Silodosin (n=71)	1777 (573)	1862 (610)	1569** (583)	1633** (634)	1652** (564)
Total (n=141)	1846 (672)	1866 (680)	1675** (576)	1676** (642)	1670** (561)
24-hour urinary frequency					
Naftopidil (n=70)	9.2 (2.4)	12.0** (3.9)	12.6** (3.9)	11.4** (3.7)	10.0** (2.5)
Silodosin (n=71)	9.2 (2.4)	12.3** (3.5)	11.8** (3.1)	11.2** (3.6)	10.3** (3.2)
Total (n=141)	9.2 (2.4)	12.2** (3.7)	12.2** (3.5)	11.3** (3.6)	10.1** (2.9)
Mean voided vol (mL)					
Naftopidil (n=70)	215 (84)	165** (66)	151** (60)	157** (58)	177** (71)
Silodosin (n=71)	199 (66)	159** (56)	140** (57)	153** (55)	168** (64)
Total (n=141)	207 (76)	162** (61)	145** (58)	155** (57)	173** (67)

*$p < 0.05$, **$p < 0.01$.

Table 6 The univariate and multivariate analyses predicting IPSS recovery at 12 months after seed implantation

	Univariate		Multiivariate		
	p-value	Odds ratio	*p*-value	Odds ratio	95% C.I.
Neo-ADT	0.081	0.510	n.s.		
EBRT	0.036	2.367	n.s.		
PV at post-dosimetry (mL)	0.066	0.957	n.s.		
D90(Gy)	0.018	0.984	n.s.		
UD30(Gy)	0.008	0.986	0.006	0.986	0.957-0.996

Neo ADT: neoadjuvant androgen deprivation therapy, EBRT: external beam radiation therapy, PV: prostate volume, D90: minimal dose (Gy) received by 90% of the prostate gland, UD30: minimal dose (Gy) received by 30% of the urethra.



World J Urol (2014) 32:1423–1432
DOI 10.1007/s00345-014-1239-z

ORIGINAL ARTICLE

Efficacy of silodosin in patients undergoing brachytherapy: a randomized trial involving a pressure flow study

Nobutaka Shimizu · Takafumi Minami · Koichi Sugimoto · Yoshitaka Saito · Yutaka Yamamoto · Taiji Hayashi · Hidenori Tsuji · Masahiro Nozawa · Kazuhiro Yoshimura · Tokumi Ishii · Hirotsugu Uemura · Kiyoshi Nakamatsu

Against the use

LE: 1+ GR: B

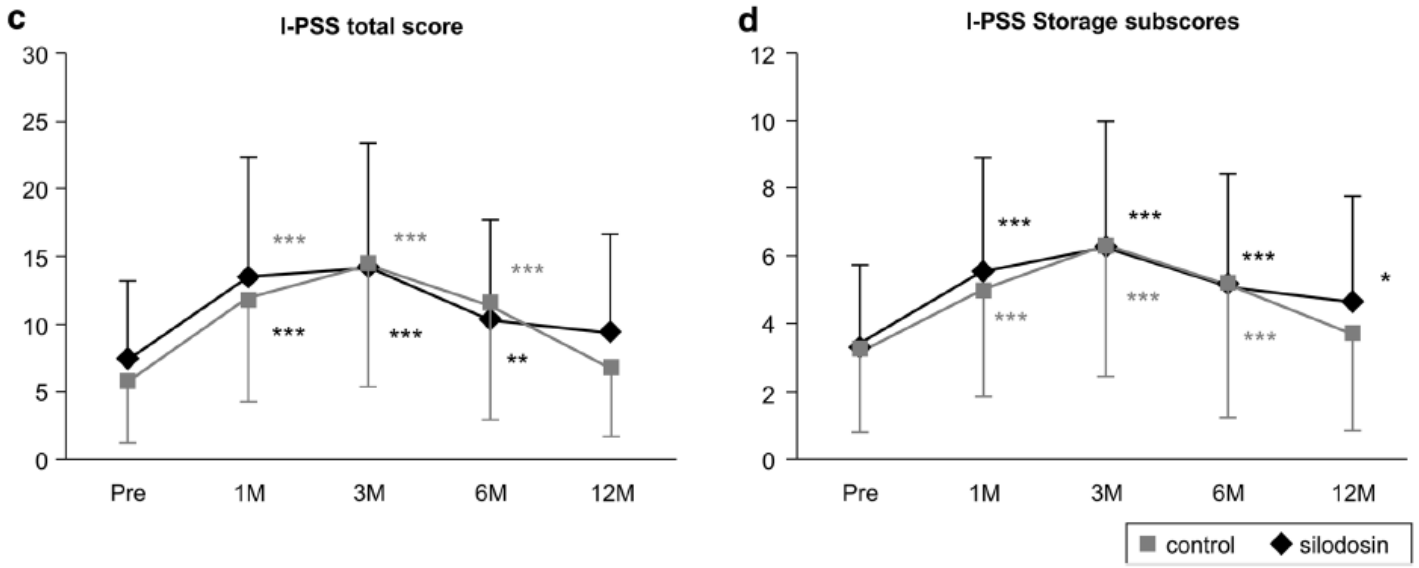
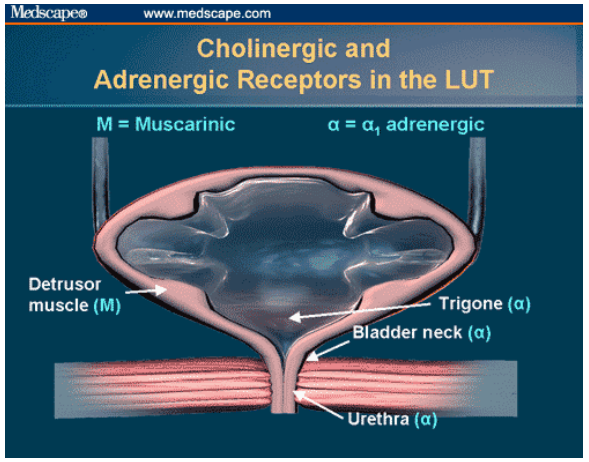


Fig. 3 Time course of prostate-specific antigen (*PSA*), prostate volume, International Prostate Symptom Score (*I-PSS*), and I-PSS storage subscores. Wilcoxon signed-rank test versus preoperative values. Mean ± SD, $*p < 0.05$; $**p < 0.01$; $***p < 0.001$



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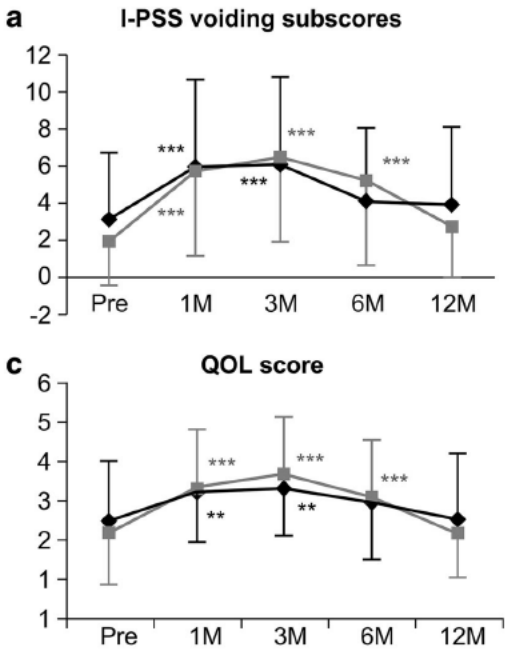


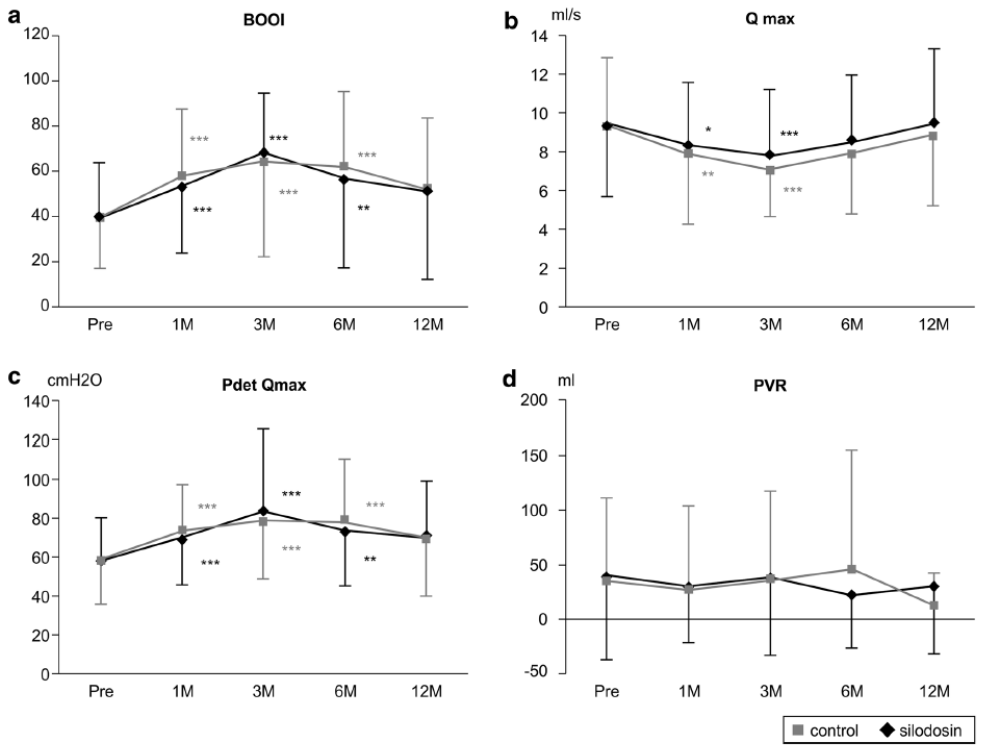
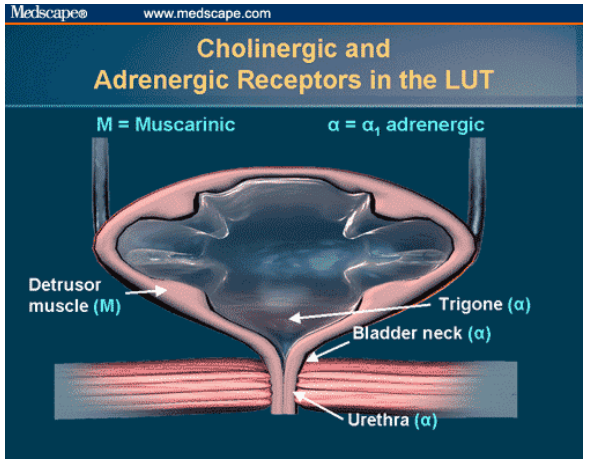


Fig. 5 Time course of voiding function. *BOOI* bladder outlet obstruction index, *Qmax* maximal urinary flow rate, *PdetQmax* detrusor pressure at Qmax, *PVR* post-void residual urine. Wilcoxon signed-rank test versus preoperative values. Mean ± SD, $*p < 0.05$; $**p < 0.01$; $***p < 0.001$



ELSEVIER

In favor of use

LE: 2+ GR: C

PROPHYLACTIC VERSUS THERAPEUTIC ALPHA-BLOCKERS AFTER PERMANENT PROSTATE BRACHYTHERAPY

GREGORY S. MERRICK, WAYNE M. BUTLER, KENT E. WALLNER, JONATHAN H. LIEF, AND ROBERT W. GALBREATH

TABLE I. *Patient clinical and treatment parameters stratified by alpha-blocker status*

Parameter	Overall	Therapeutic Alpha-Blocker	Prophylactic Alpha-Blocker	*P* Value
Patients (n)	234	101	133	
Age at implant (yr)	66.4 ± 6.6	66.4 ± 6.9	66.3 ± 6.5	0.898
US prostate volume (cm^3)	32.8 ± 9.5	28.7 ± 10.2	35.7 ± 7.8	<0.001*
V_{200} (% volume)†	40 ± 13	40 ± 14	40 ± 8	0.432
V_{100} (% volume)†	87 ± 10	85 ± 10	97 ± 4	<0.001*
D_{90} (% Rx)†	96 ± 27	91 ± 26	123 ± 12	<0.001*
Maximal urethral dose (% Rx)†‡	149 ± 24		149 ± 24	
Mean urethral dose (% Rx)†‡	127 ± 18		127 ± 18	
Follow-up (mo)	8.7 ± 4.6	10.2 ± 4.9	7.5 ± 4.1	<0.001*

KEY: US = ultrasound; V_{200}, V_{100} = percentage of prostate volume receiving 200% and 100% of prescribed minimal peripheral dose; D_{90} = minimal dose received by 90% of prostate gland.
** Statistically significant.*
† Day 0 computed tomography-based dosimetry.
‡ Urethral dosimetry was not obtained at the Puget Sound Health Care System (Seattle).

TABLE II. *Patient clinical and treatment parameters stratified by implant protocol*

Parameter	Overall	Monotherapy	Combined Modality	*P* Value
Patients (n)	234	136	98	
Age at implant (yr)	66.4 ± 6.6	66.5 ± 6.5	66.1 ± 6.9	0.669
US prostate volume (cm^3)	32.8 ± 9.5	33.9 ± 10.0	31.3 ± 8.7	0.043*
V_{200} (% volume)†	40 ± 13	38 ± 13	42 ± 14	0.160
V_{100} (% volume)†	87 ± 10	88 ± 9	83 ± 12	0.014*
D_{90} (% Rx)†	96 ± 27	99 ± 26	90 ± 28	0.116
Maximal urethral dose (% Rx)†‡	149 ± 24	145 ± 25	154 ± 22	0.032*
Mean urethral dose (% Rx)†‡	127 ± 18	125 ± 20	130 ± 15	0.144
Follow-up (mo)	8.7 ± 4.6	9.9 ± 4.9	6.9 ± 3.6	<0.001*

KEY: US = ultrasound; V_{200}, V_{100} = percentage of prostate volume receiving 200% and 100% of prescribed minimal peripheral dose; D_{90} = minimal dose received by 90% of prostate gland.
** Statistically significant.*
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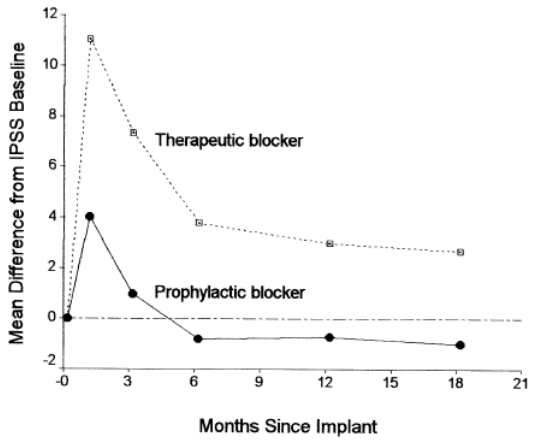

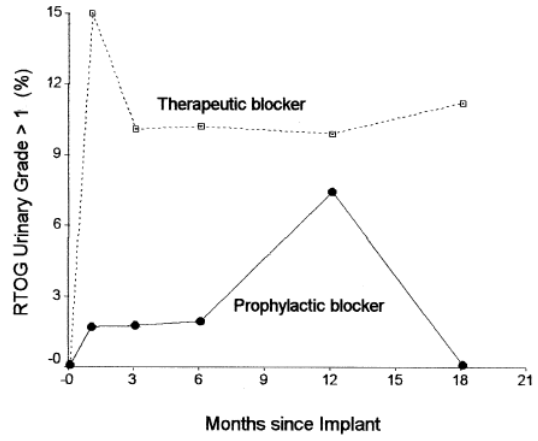

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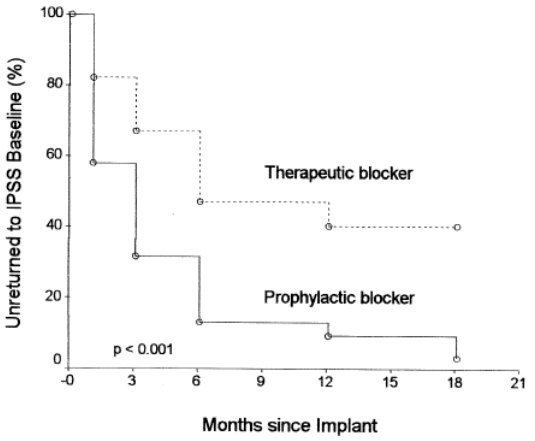


Haemorragic radiation cystitis

Medical treatment for radiation-induced hemorrhagic cystitis

Drug And Route	Dose	Pharmacology	Common Adverse events	Clinical Results	Level of evidence	Grade of recommendation	
Oral/IV							
Pentosan Polysulfate	100 mg oral three times day	Protective coating on bladder wall	Diarrhea, dyspepsia	CR: 71%	2+	D	
WF10	0,5/0,75 mg/Kg in 250 ml over no less than 1h for 5 consecutive days	Immune modulation, inhibition of inflammatory response	Tachycardia, phlebitis (for rapid infusion)	CR: 74%-88% RR: 24%-47%	1+	B	
Topical							
Formalin	1% solution passively irrigated for 20-30 min following by saline irrigation (12-48h)	Capillary occlusion and protein fixation at the level of urothelium	Mild fever, frequency, dysuria, suprapubic pain	CR: 75%-89% RR: 23%	2+	D	
Hyaluronic acid	Solution instilled and retained for 20 min. Weekly in the first month and then monthly in the following 2 months	Restores the damaged glycosaminoglycan layer and decreases the bacterial adherence	Urinary tract infection due to repeated urethral catheterization	CR: 88%-100% RR: 25%	1+	B	
Hyperbaric O_2	2-2.5 atm, 90 min approximately	NA	Diarrhea, dyspepsia	CR: 59-96% RR: 16%-34%	2+	C	

Intensity Modulated Radiation Therapy (IMRT)
And
Image Guided Radiation Therapy

A new effective way to reduce GU toxicity ?

Original Article Cancer July 1, 2016

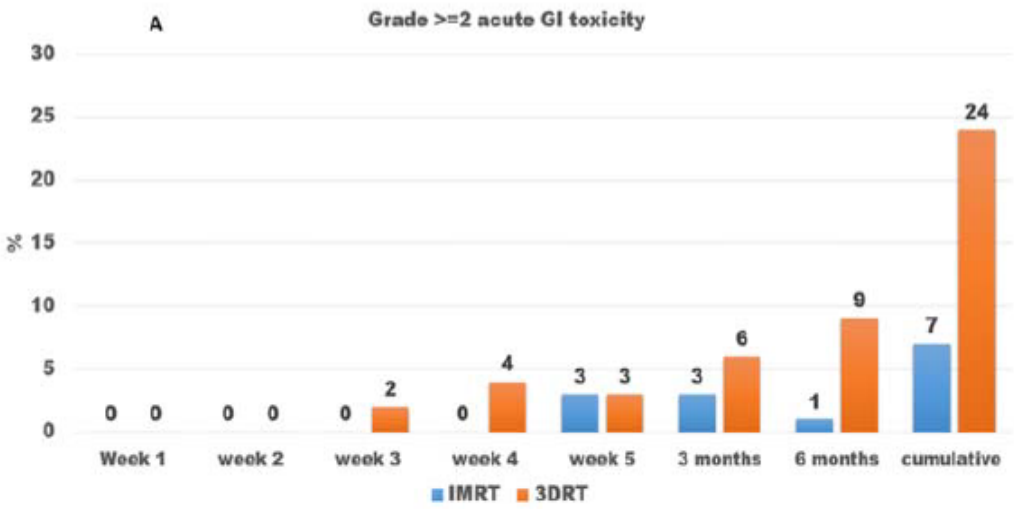
Intensity-Modulated Radiotherapy Reduces Toxicity With Similar Biochemical Control Compared With 3-Dimensional Conformal Radiotherapy for Prostate Cancer: A Randomized Clinical Trial

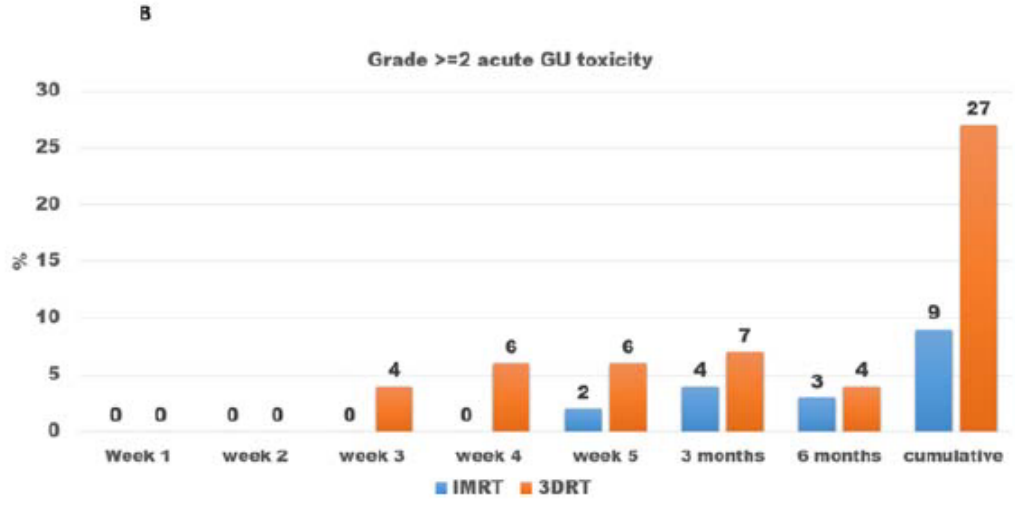
Gustavo Arruda Viani, MD, PhD; Bruno Silveira Viana, MD; Jose Eduardo Chicareli Martin, MD; Bruno Tiago Rossi, MedPhys; Gisele Zuliani, MD; and Eduardo Jose Stefano, MD

In favor of use

LE: 1+ GR: B

Radiation Treatment: 70 Gy in 25 fractions is equivalent to 86 Gy in 43 fractions





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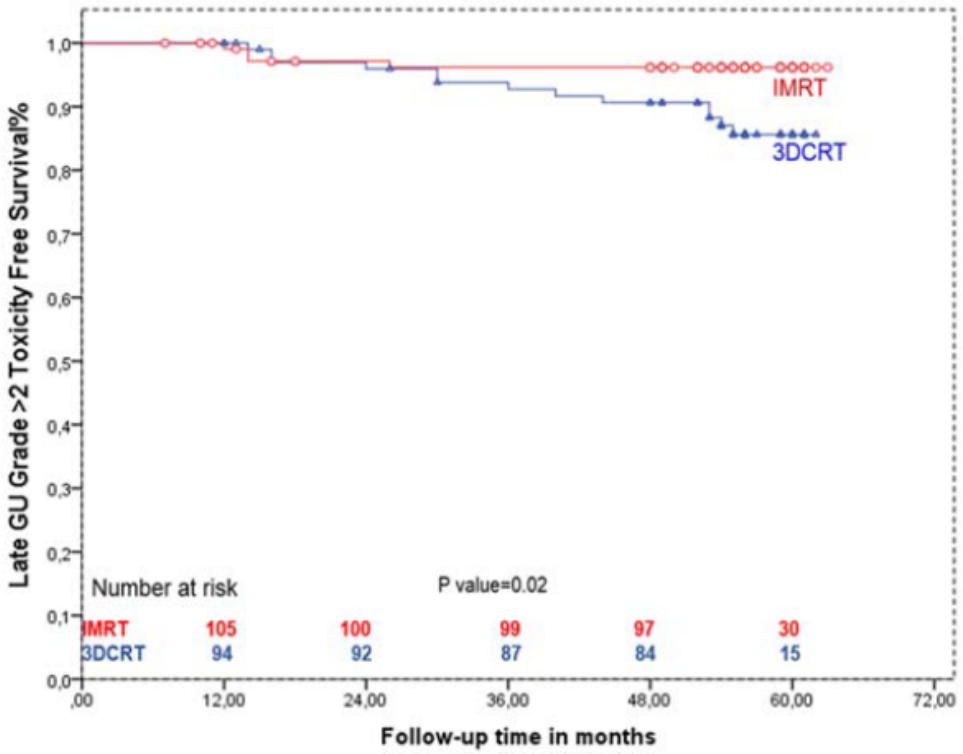

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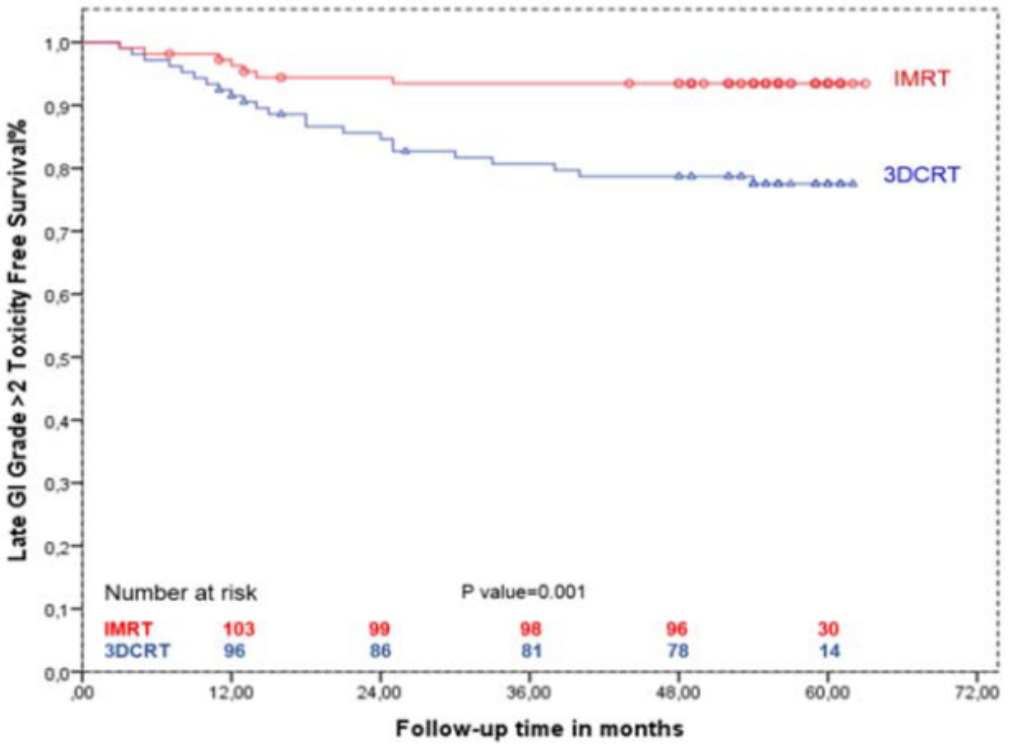


Comparison of Toxicity Outcomes Between IGRT and IMRT

(Zelefsky et al IJROBP- 2012)

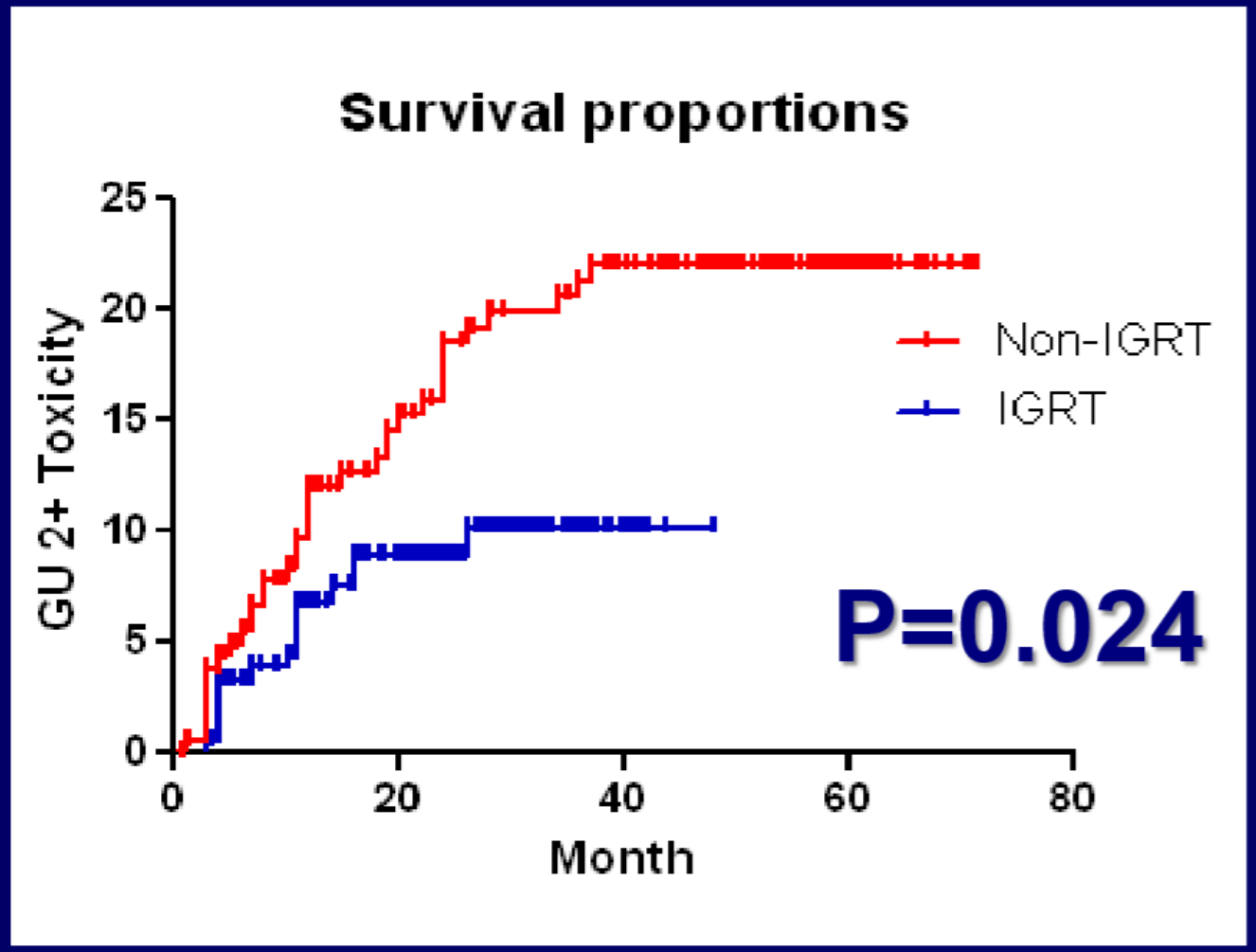
Characteristics	Non-IGRT (N=190) 2006-2008	IGRT (N=186) 2008-2010
Radiation Dose	86.4 Gy	86.4 Gy
CTV-PTV Margins	1 cm except at prostate rectal interface where 6 mm margin used	1 cm except at prostate rectal interface where 6 mm margin used
Use of Androgen Deprivation Therapy	54%	42%
Median IPSS Score	9	9

In favor of use

2++ B

Comparison of Toxicity Outcomes Between IGRT and IMRT

(Zelefsky et al IJROBP- 2012)



In favor of use

2++ B

Conclusions

1. Alpha1-blocking receptors:
    a. Conflicting data in the management of men treated with **brachytherapy.**
    b. **No** direct evidence for **EBRT**
    c. These drugs are more effective when used **prophylactically**

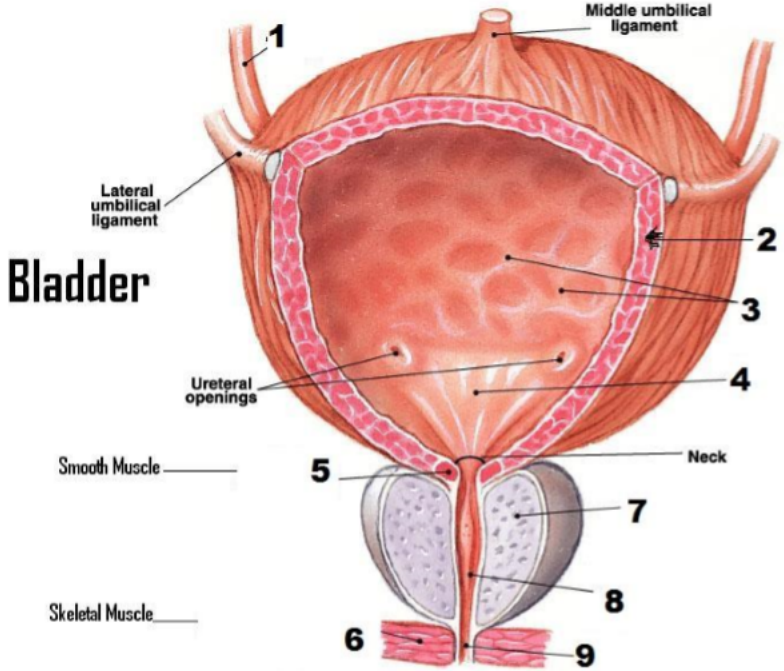
2. Solifenacin may be reasonably used in the management of men treated **with EBRT. No** evidence on **brachytherapy**

3. **WF10, Hyaluronic acid and Hyperbaric** oxygen may be useful in **hemorrhagic cystitis**

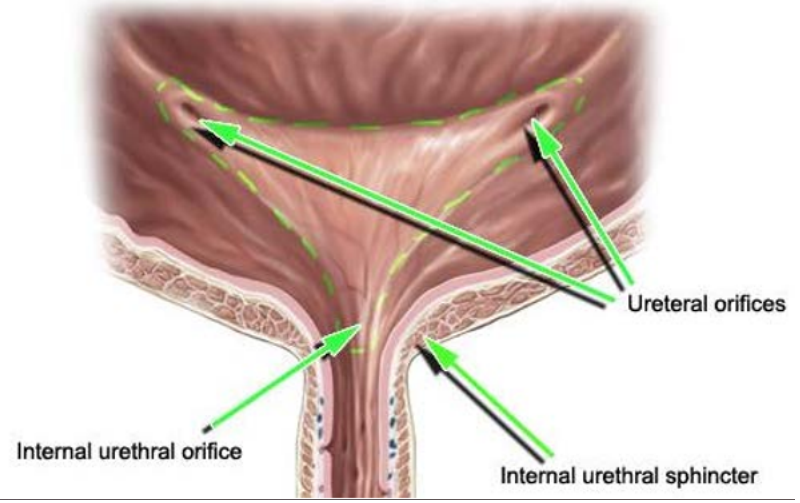
4. There is level 1 evidence that prostate IMRT reduces GU toxicity in **hypofractionated regimens** with a potential further improvement with the use of IGRT

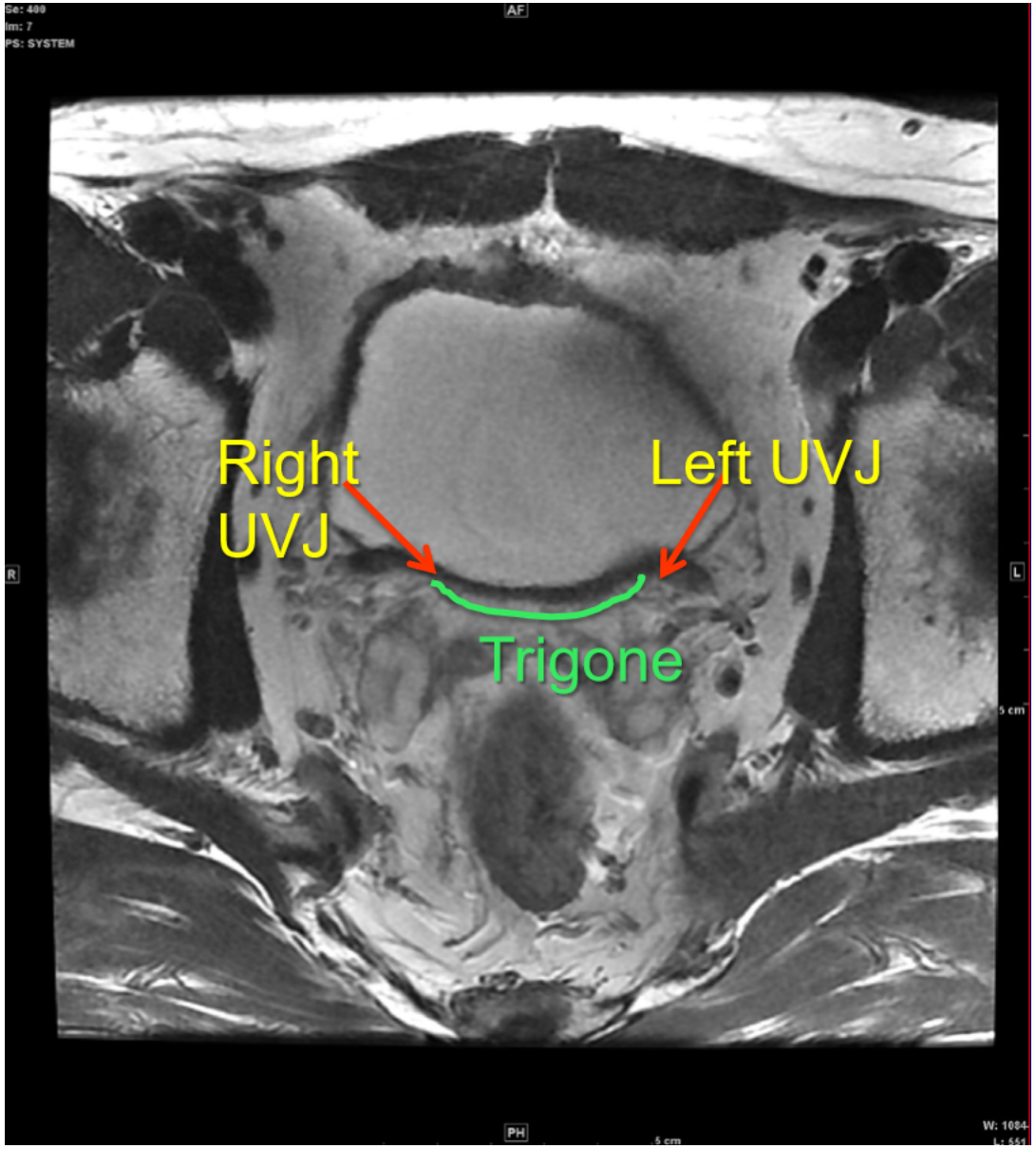
Role of the Bladder Trigone in Micturition

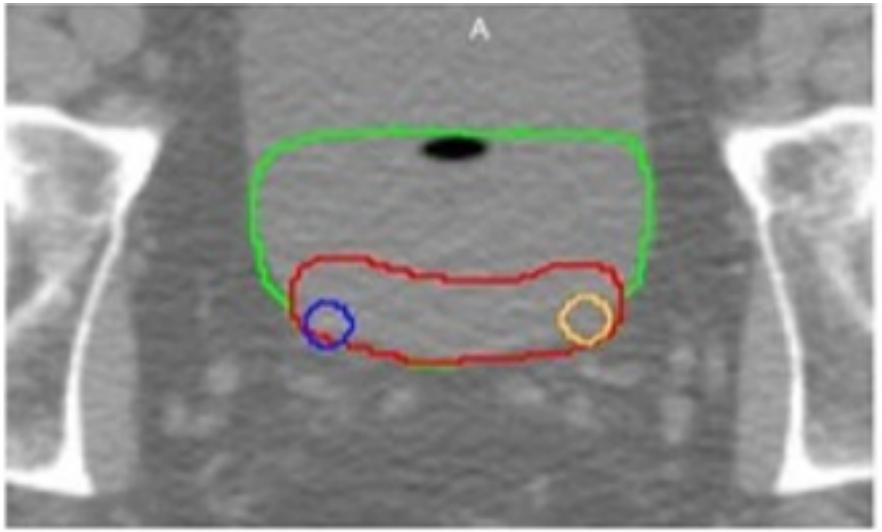
- Trigone contracts during bladder filling which helps keep the ureteral orifices open and the bladder neck shut.
- When micturition occurs, trigone musculature relaxes and urine is funneled into the urethra.
- RT may affect urothelial smooth muscle or vasculature or possibly negatively impact on nerve activation changes especially in the region of the trigone.



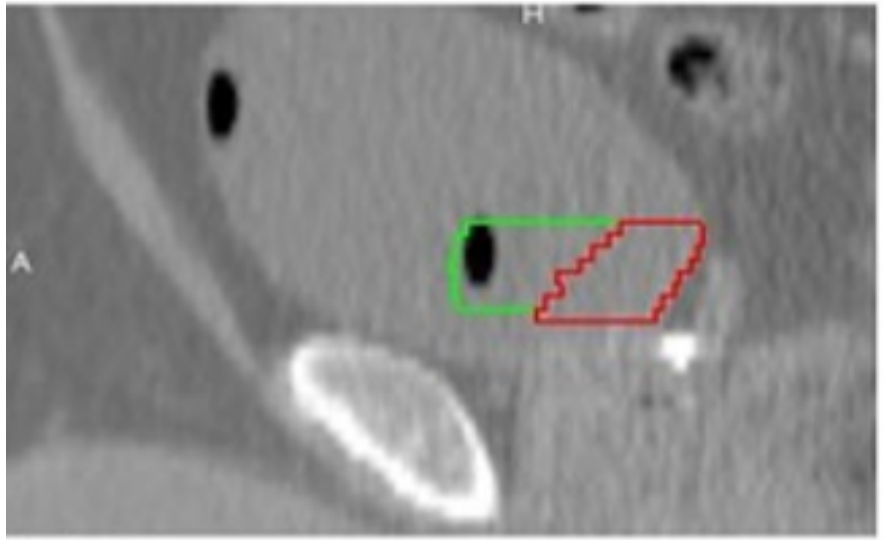
Contouring the bladder trigone







(A) including left ureter (orange) and right ureter (blue)



(B)

Delineate the Bladder Neck to Constrain the Dose to this Region

- **Dose to the bladder neck is the most important predictor for acute and late toxicity after low-dose-rate prostate brachytherapy: implications for establishing new dose constraints for treatment planning.**

  Hathout L, Folkert MR, Kollmeier MA, Yamada Y, Cohen GN, Zelefsky MJ.
  Int J Radiat Oncol Biol Phys. 2014

- **Impact of dose to the bladder trigone on long-term urinary function after high-dose intensity modulated radiation therapy for localized prostate cancer.**

  Ghadjar P, Zelefsky MJ, Spratt DE, Munck af Rosenschöld P, Oh JH, Hunt M, Kollmeier M, Happersett L, Yorke E, Deasy JO, Jackson A.
  Int J Radiat Oncol Biol Phys. 2014

Recommendations on nonoperative treatment of Peyronie's disease

	LE	GR
Conservative treatment for Peyronie's disease is primarily aimed at treating patients in the early stage of disease. It is an option in patients not fit for surgery or when surgery is not acceptable to the patient.	3	C
Oral treatment with potassium para-aminobenzoate may result in a significant reduction in penile plaque size and penile pain as well as penile curvature stabilisation.	1b	B
Intralesional treatment with verapamil may induce a significant reduction in penile curvature and plaque volume.	1b	C
Intralesional treatment with clostridial collagenase showed significant decreases in the deviation angle, plaque width, and plaque length.	2b	C
Intralesional treatment with interferon may improve penile curvature, plaque size and density, and pain.	1b	B
Topical verapamil gel 15% may improve penile curvature and plaque size.	1b	B
Iontophoresis with verapamil 5 mg and dexamethasone 8 mg may improve penile curvature and plaque size.	1b	B

Recommendations against treatment

	LE	GR
Intralesional treatment with steroids is not associated with a significant reduction in penile curvature, plaque size, or penile pain, and intralesional treatment with steroids can therefore not be recommended.	1b	B
Oral treatment with vitamin E and tamoxifen are not associated with significant reduction in penile curvature, plaque size, or penile pain and therefore should not be used for this purpose.	2b	B
Other oral treatments (acetyl esters of carnitine, pentoxifylline) are not recommended.	3	C

LE = level of evidence; GR = grade of recommendation.

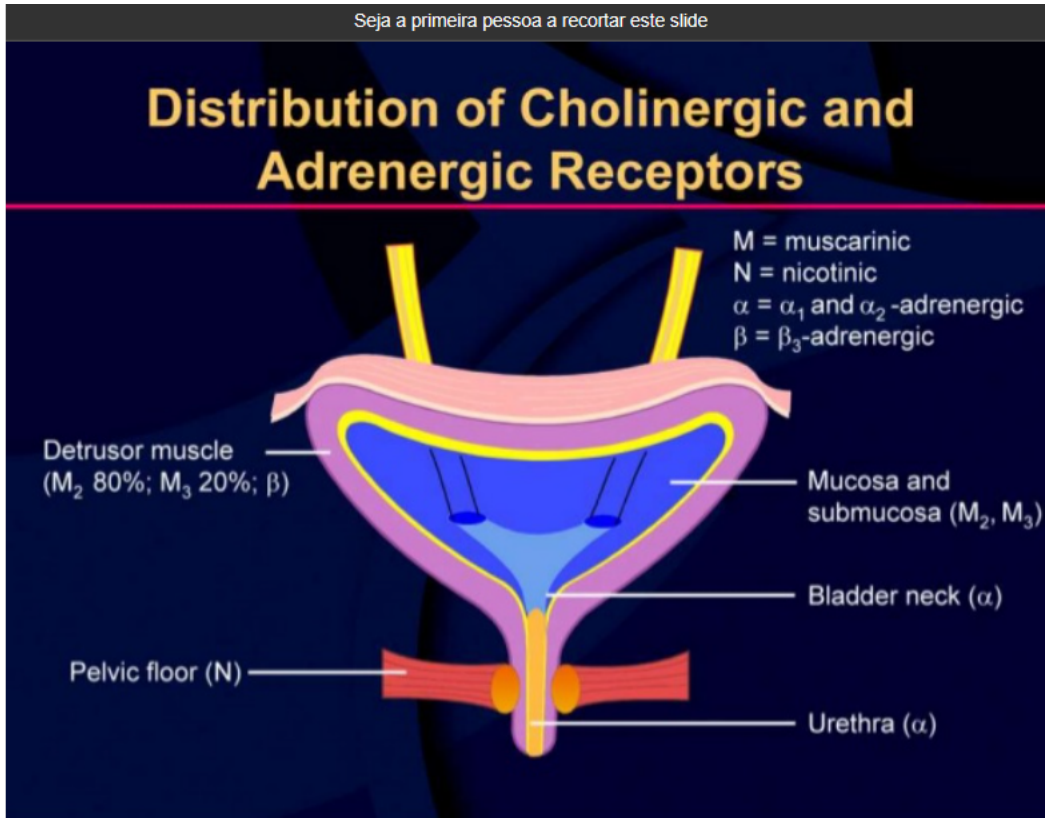
Table 1. Drugs used for the treatment of overactive bladder.

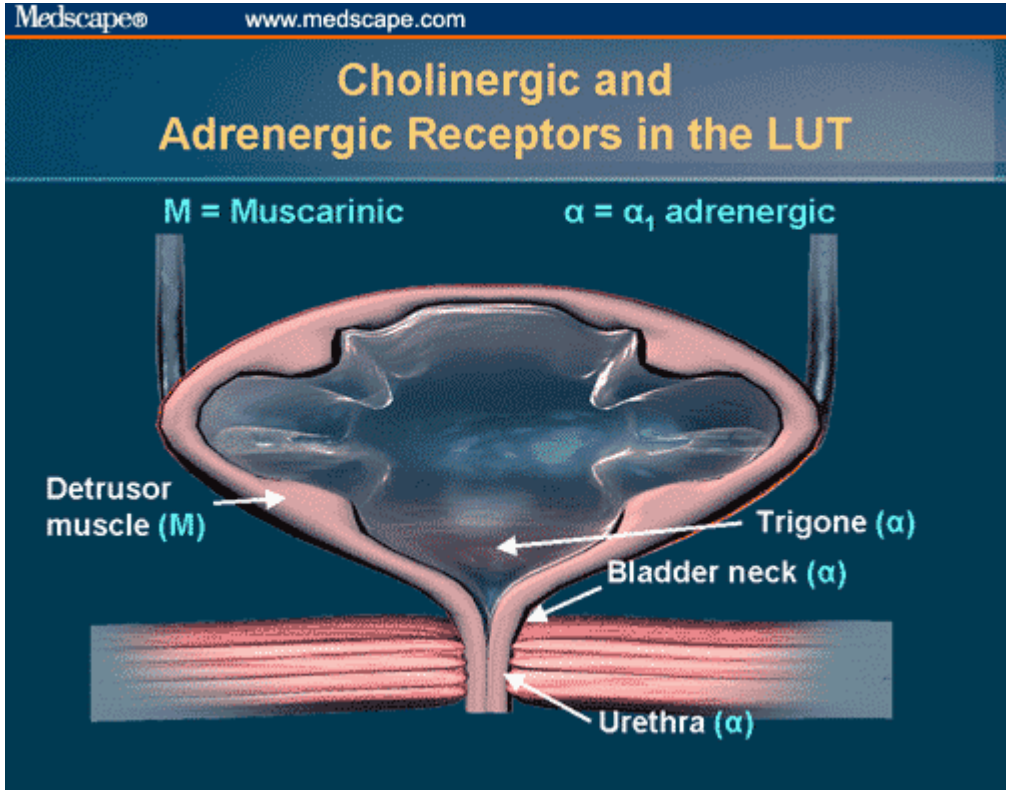
Drug	Level of evidence*	Grade of recommendation‡
Tolterodine	1	A
Trospium	1	A
Solifenacin	1	A
Darifenacin	1	A
Propantheline	2	B
Atropine	3	C
Oxybutinin	1	A
Propiverine	1	A
Dicyclomine	3	C
Flavoxate	2	D
Imipramine	3	C

**1: Systematic reviews, meta-analysis, good quality randomized controlled trials; 2: Randomized, controlled trials, good quality prospective cohort studies; 3: Case–control studies, case series.*

‡A: Based on level 1 evidence (highly recommended); B: Consistent level 2 or 3 evidence (recommended); C: Level 4 studies or 'majority evidence' (optional); D: Evidence inconsistent/inconclusive (no recommendation possible).

Adapted from the International Consultation on Incontinence report, 2004 [6].

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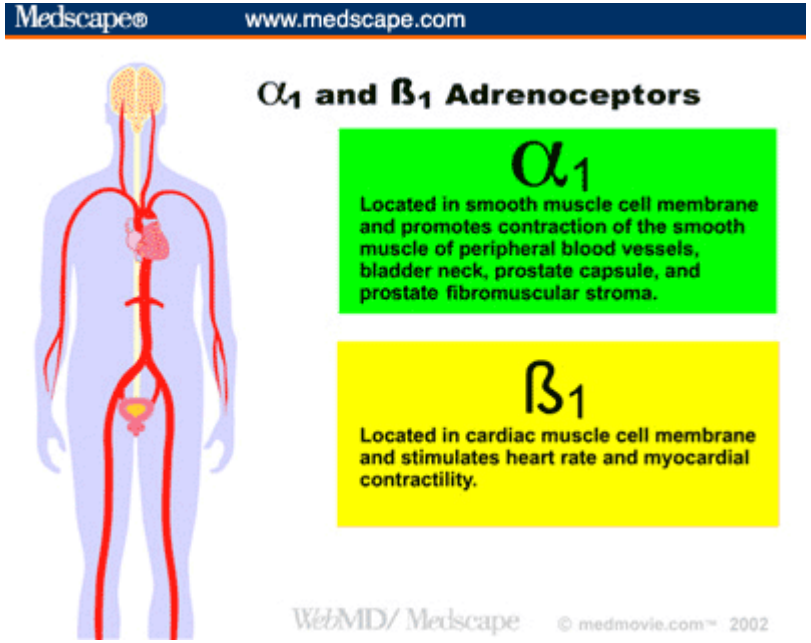
Cholinergic and
Adrenergic Receptors in the LUT
M = Muscarinic
α = α1 adrenergic
Detrusor
muscle (M)
Trigone (α)
Bladder neck (α)
Urethra (α)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α1 and ß1 Adrenoceptors
α1
Located in smooth muscle cell membrane and promotes contraction of the smooth muscle of peripheral blood vessels, bladder neck, prostate capsule, and prostate fibromuscular stroma.
ß1
Located in cardiac muscle cell membrane and stimulates heart rate and myocardial contractility.
WebMD/ Medscape
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Bladder

Bladder GAG Layer/Epithelial Permeability

- **It has been hypothesized that radiation cystitis is the result of some defect in the epithelial permeability barrier of the bladder surface glycosaminoglycans**

- Major classes of glycosaminoglycans (GAGs) include *hyaluronic acid, heparin sulfate, heparin*, chondroitin 4-sulfate and chondroitin 6-sulfate, dermatan sulfate, and keratan sulfate

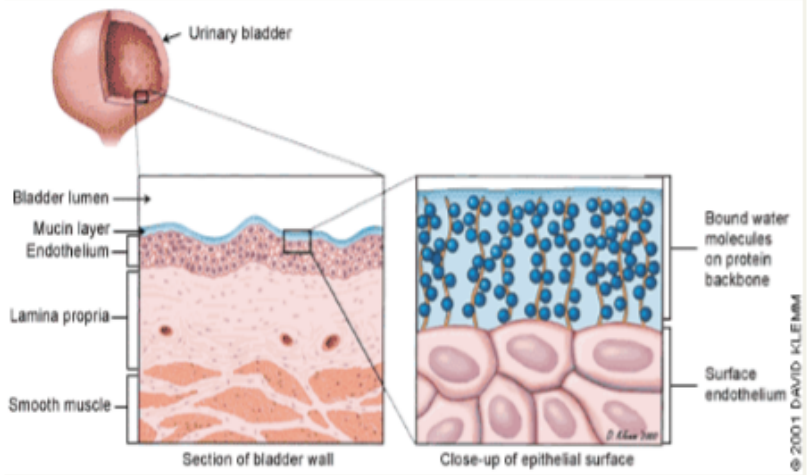

Figure 1. A Depiction of Normal and Abnormal Bladder Epithelium