

Obniżenie dawek w promieniowrażliwych narządach krytycznych poprzez łączenie teleradioterapii i brachyterapii w raku gruczołu krokowego. Praktyczne aspekty planowania skojarzonej radioterapii .

Lek. Artur Chyrek
Zakład Brachyterapii
Wielkopolskie Centrum Onkologii
Warszawa 17.11.2018

ASCENDE-RT:

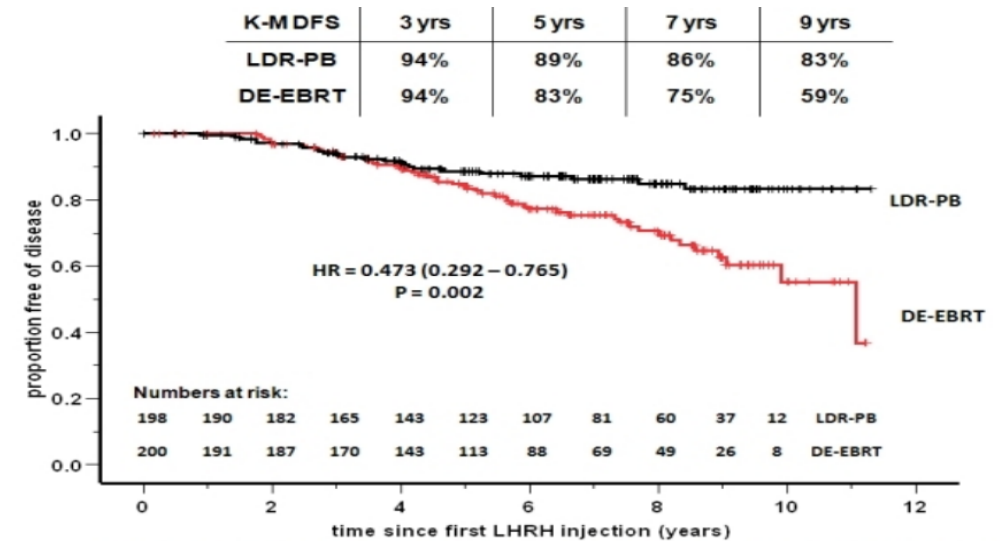
Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy is an NCI registered trial (NCT00175396)

- 398 pts (High i Inter PCa)
- ADT przez 12 msc
- Po 8 msc – EBRT do 46 Gy

Dose Escalation

n= 200 pts
32 Gy 16 fx
TD = 78 Gy

LDR –PB n=198
1125 BTh = 115Gy



K-M disease free survival using the nadir+2 ng/mL threshold for biochemical failure

Conclusions: In multi-centre randomized setting, an LDR-PB boost demonstrated a large advantage over a DE-EBRT boost in relation to the primary endpoint (DFS). To date, OS and prostate cancer-specific survival do not appear to differ between arms. However, existing trends favour LDR-PB, suggesting differences in these survival endpoints may well emerge with longer FU.

Using a surgical prostate-specific antigen threshold of >0.2 ng/mL to define biochemical failure for intermediate- and high-risk prostate cancer patients treated with definitive radiation therapy in the ASCENDE-RT[†] randomized control trial

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Clinical Investigation

ASCENDE-RT: An Analysis of Treatment-Related Morbidity for a Randomized Trial Comparing a Low-Dose-Rate Brachytherapy Boost with a Dose-Escalated External Beam Boost for High- and Intermediate-Risk Prostate Cancer

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and Nevin Murray, MD, FRCPC^{*,**}

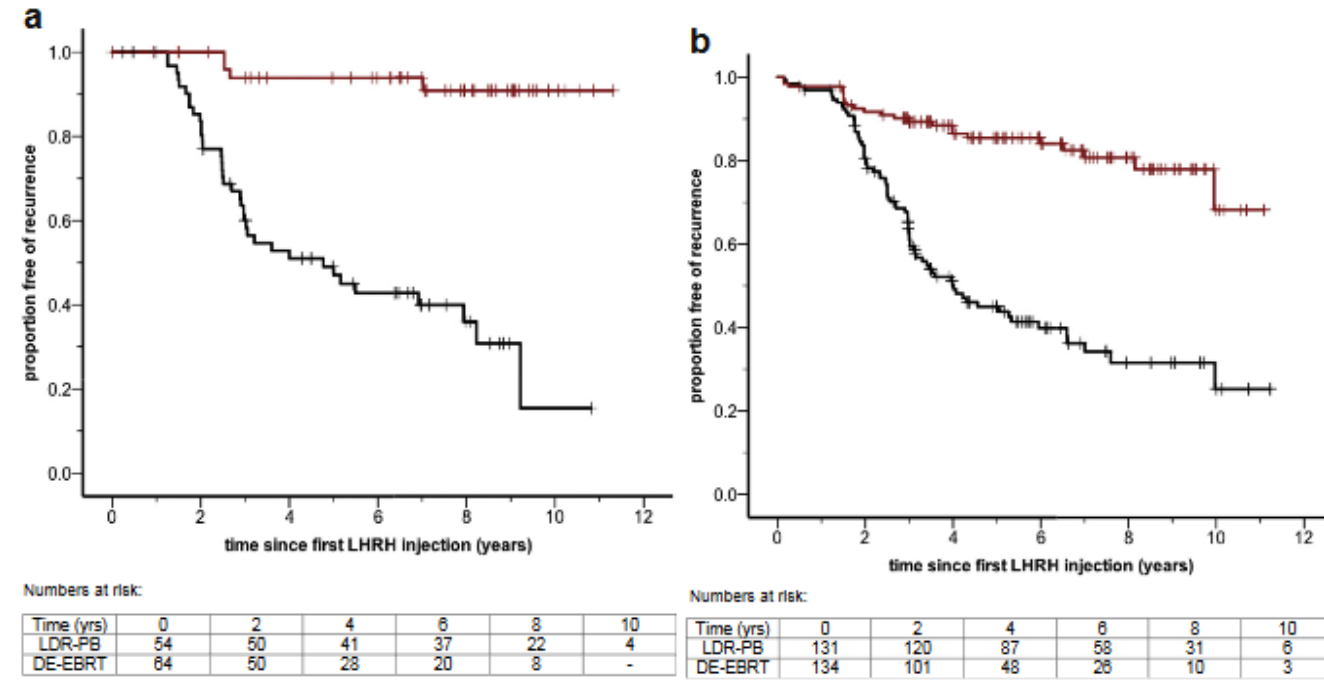
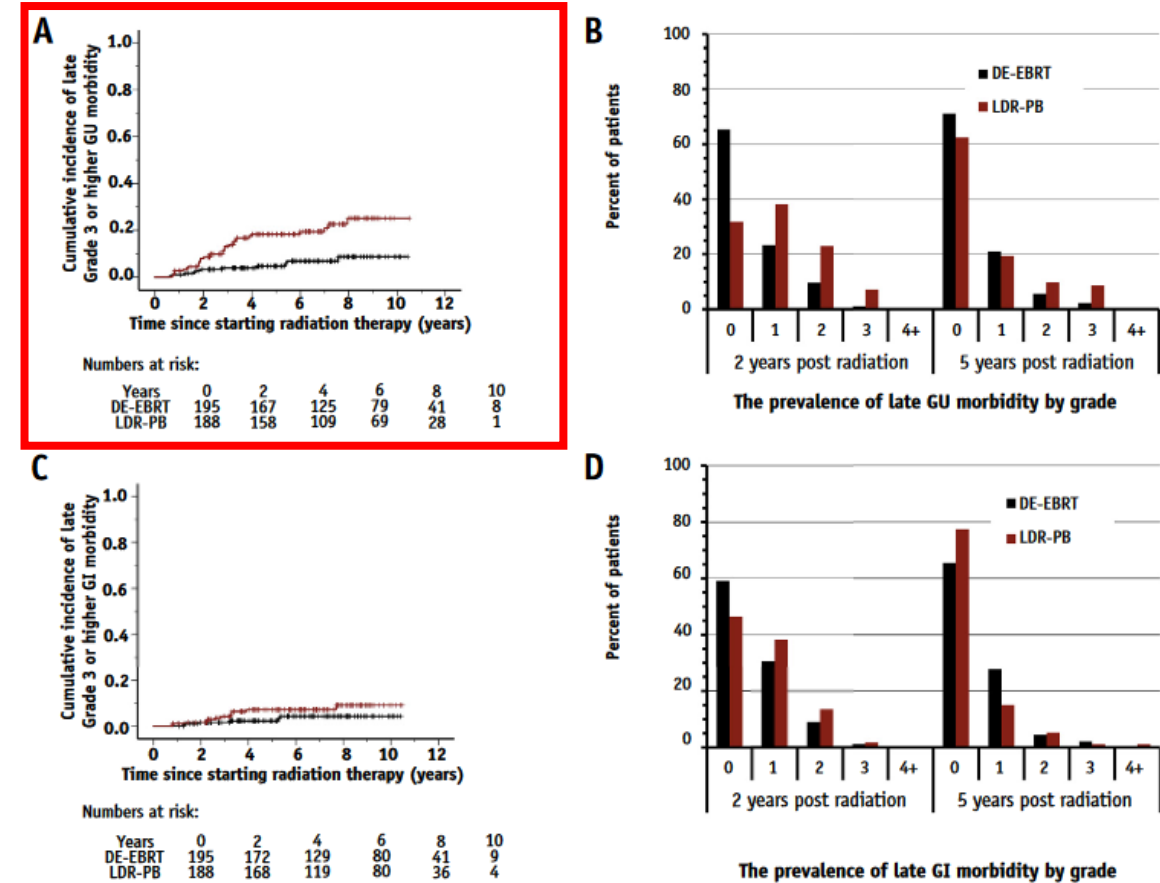


Fig. 3. (a) Intermediate-risk subgroup: Kaplan-Meier plots comparing b-PFS for LDR-PB boost (upper [red] line) with DE-EBRT boost (lower [black] line) using a surgical definition of biochemical failure of >0.2 ng/mL. (log rank $p < 0.001$). (b) High-risk subgroup: Kaplan-Meier plots comparing b-PFS for LDR-PB boost (upper [red] line) with DE-EBRT boost (lower [black] line) using a surgical definition of biochemical failure of >0.2 ng/mL (log rank $p < 0.001$). b-PFS = biochemical progression free survival; LDR-PB = low-dose-rate prostate brachytherapy boost; DE-EBRT = dose-escalated external beam radiation therapy.



Phase III randomised trial

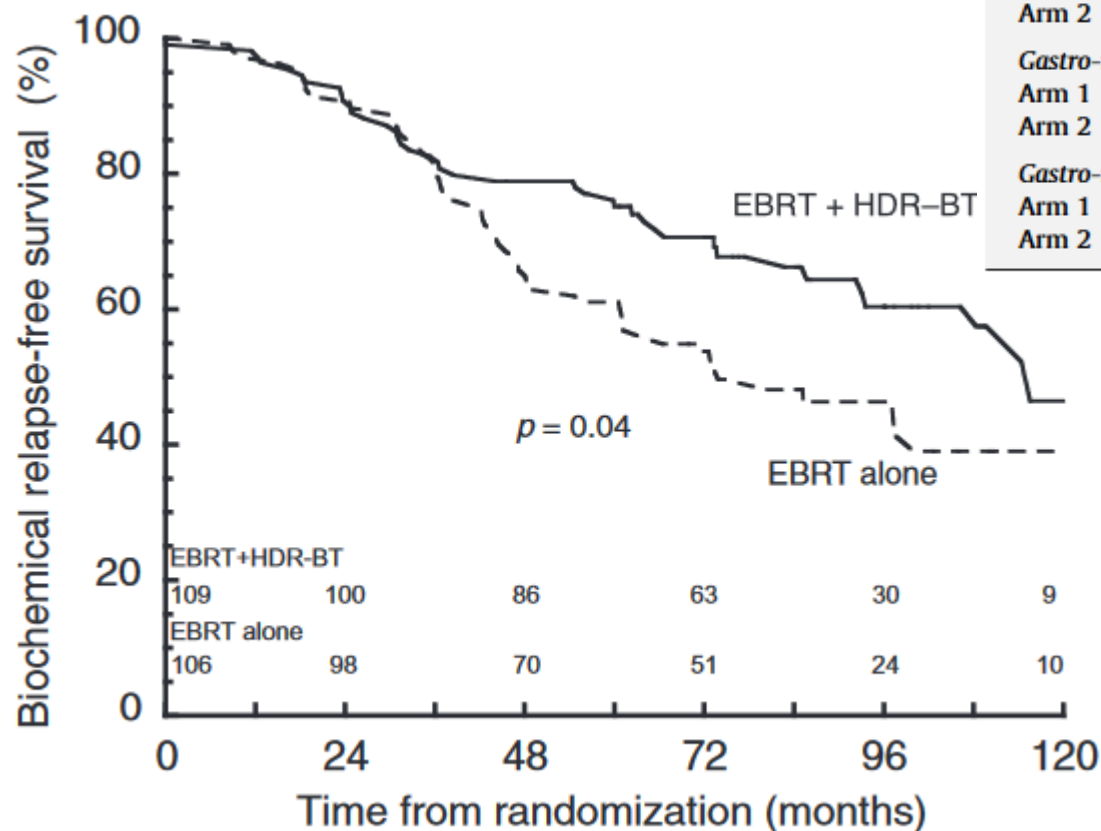
Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer

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- RCT III -218 pts, cT1-3, iPSA < 50 ng/ml
- EBRT – 55 Gy/20 fx vs
- EBRT 37,5 Gy + HDR 2 x 8,5 Gy
- OS - ns

Toksyczność n.s.

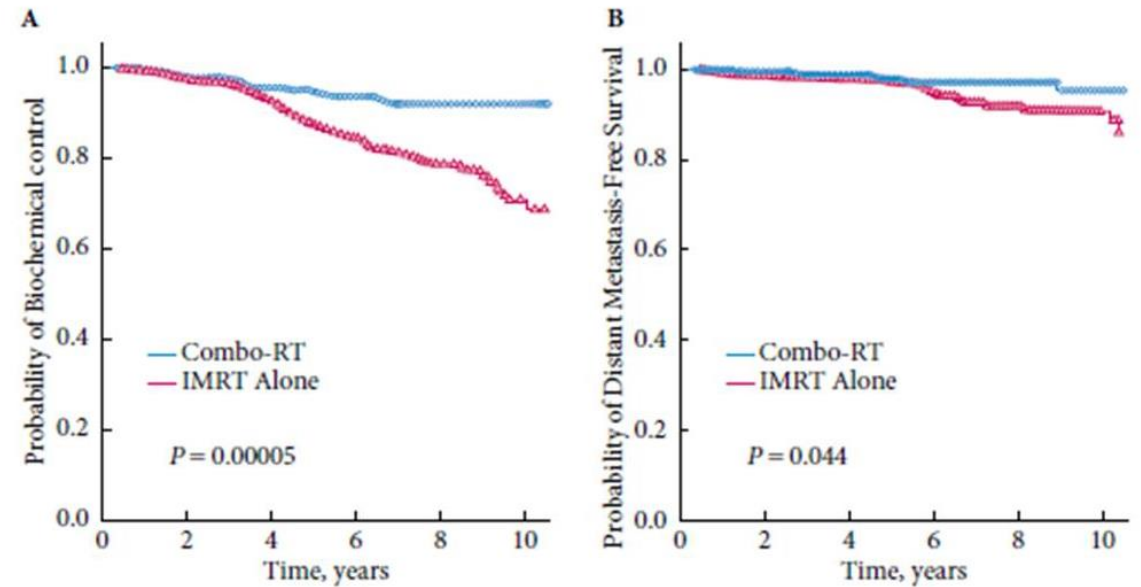
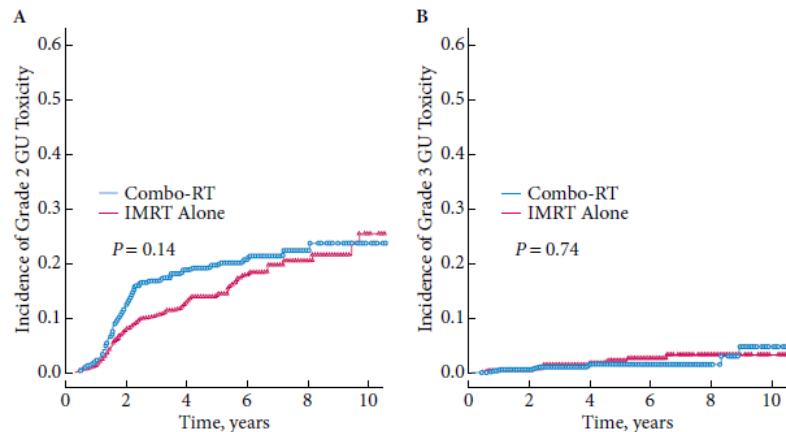
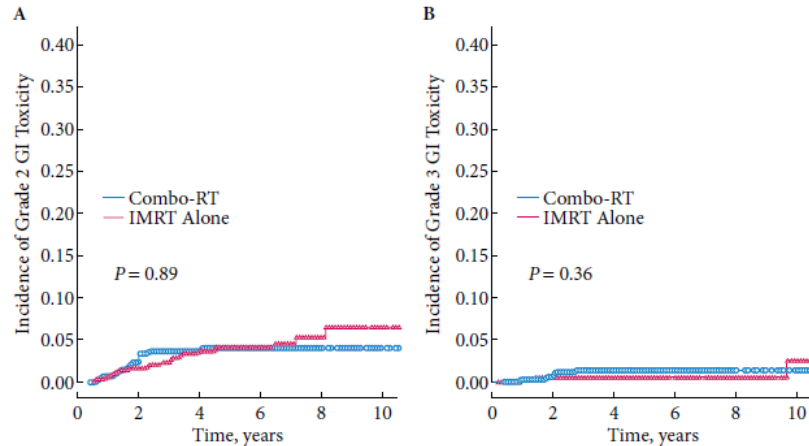


Endpoint	Analytical procedure	At 5 years	At 7 years	p value
<i>bRFS</i>				0.04
Arm 1	K-M	61%	48%	
Arm 2		75%	66%	
<i>OS</i>				0.2
Arm 1	K-M	89%	88%	
Arm 2		88%	81%	
<i>Genito-urinary</i>				0.5
Arm 1	K-M	26%	30%	
Arm 2		26%	31%	
<i>Genito-urinary</i>				5 year: 1.0 7 year: 0.4
Arm 1	Prevalence	9%	4%	
Arm 2		8%	11%	
<i>Urethral strictures</i>				0.1
Arm 1	K-M	2%	2%	
Arm 2		6%	8%	
<i>Gastro-intestinal</i>				0.8
Arm 1	K-M	6%	6%	
Arm 2		7%	7%	
<i>Gastro-intestinal</i>				7 year: 1
Arm 1	Prevalence	0%	2%	
Arm 2		0%	0%	

Comparison of high-dose (86.4 Gy) IMRT vs combined brachytherapy plus IMRT for intermediate-risk prostate cancer

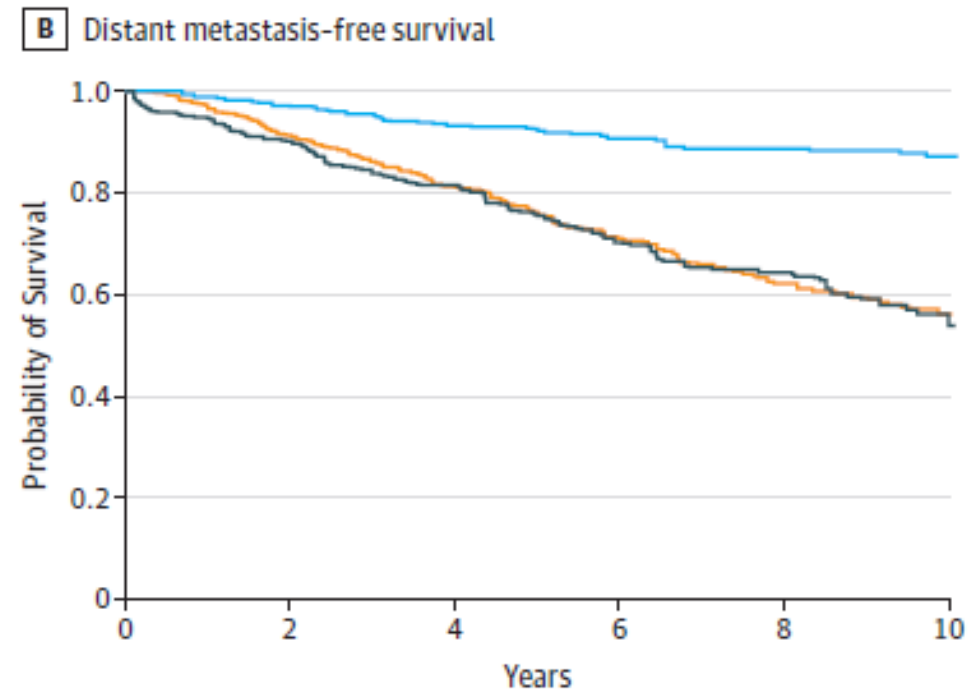
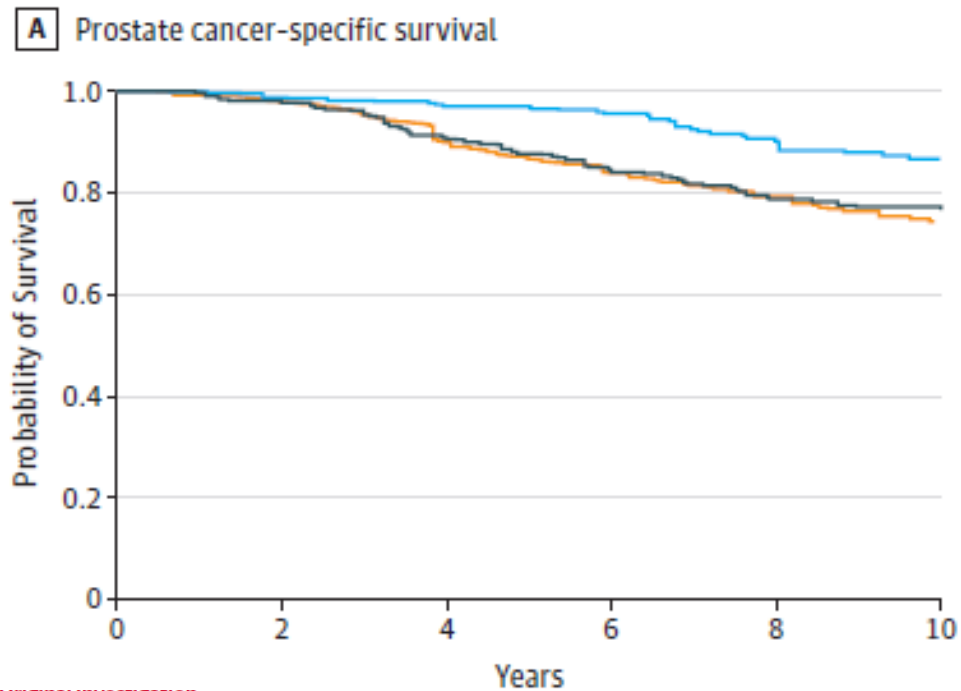
Daniel E. Spratt, Zachary S. Zumsteg, Pirus Ghadjar, Marisa A. Kollmeier, Xin Pei, Gilad Cohen*, William Polkinghorn, Yoshiya Yamada and Michael J. Zelefsky

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- Between 1997 and 2010, **870 patients** with **intermediate-risk prostate**
- **86.4/48fx Gy** of IMRT alone ($n = 470$) bez LN
- combo-RT consisting of brachytherapy HDR/LDR combined with 50.4 Gy of IMRT ($n = 400$).
- The **median (range) follow-up** for the entire cohort was **5.3 (1–14) years**.

Toksyczność n.s.



JAMA | Original Investigation

Radical Prostatectomy, External Beam Radiotherapy, or External Beam Radiotherapy With Brachytherapy Boost and Disease Progression and Mortality in Patients With Gleason Score 9-10 Prostate Cancer

Amar U. Kishan, MD; Ryan R. Cook, MSPH; Jay P. Ciezki, MD; Ashley E. Ross, MD, PhD; Mark M. Pomerantz, MD; Paul L. Nguyen, MD; Talha Shaikh, MD; Phuoc T. Tran, MD, PhD; Kiri A. Sandler, MD; Richard G. Stock, MD; Gregory S. Merrick, MD; D. Jeffrey Demanes, MD; Daniel E. Spratt, MD; Eyad I. Abu-Isa, MD; Trude B. Wedde, MD; Wolfgang Lilleby, MD, PhD; Daniel J. Krauss, MD; Grace K. Shaw, BA; Ridwan Alam, MPH; Chandana A. Reddy, MS; Andrew J. Stephenson, MD; Eric A. Klein, MD; Daniel Y. Song, MD; Jeffrey J. Tosoian, MD; John V. Hegde, MD; Sun Mi Yoo, MD, MPH; Ryan Flano, MPH; Anthony V. D'Amico, MD, PhD; Nicholas G. Nickols, MD, PhD; William J. Aronson, MD; Ahmad Sadeghi, MD; Stephen Greco, MD; Curtiland Deville, MD; Todd McNutt, PhD; Theodore L. DeWeese, MD; Robert E. Reiter, MD; Johnathan W. Said, MD; Michael L. Steinberg, MD; Eric M. Horwitz, MD; Patrick A. Kupelian, MD; Christopher R. King, MD, PhD

- Retrospective cohort study with 1809 patients treated between 2000 and 2013
- 639 underwent RP, 734 EBRT, and 436 EBRT+BT.
- median FU was 4.2, 5.1, and 6.3 years

Toksyczność brachyterapii HDR

Grade 3 late GU complications

Author	N	Followup (mo)	Dose	Type of treatment	Comments
Astrom (60)	214	48	10Gyx2	Boost	13 patients experienced urethral strictures
Demanes (17)	209	86	5.5 Gy–6.0Gyx4	Boost	6.7% late Grade 3 and 1% Grade 4 GU toxicity (TUR related)
Hsu (7)	112	30	9.5Gyx2	Boost	Less than 3% Grade 3 toxicity at 18 mo
Phan (49)	309	59	6Gyx4	Boost	4% late Grade 3 GU
Deger (50)	442	60	9–10 Gyx2	Boost	9% late Grade 3 GU toxicity
Martinez (77)	207	66	5.5–11Gyx2	Boost	8% late Grade 3 GU toxicity
Sullivan (52)	425	41	4–5Gyx46.5 Gyx3	Boost	8% late Grade 3 GU toxicity
Zwahlen (73)	587	66	5Gyx4–6Gyx3	Boost	7% late Grade 3 GU toxicity
Demanes (57)	298	62	7Gyx6	Mono	3% late Grade 3 GU toxicity
			9.5Gyx4		
Ghilizan (51)	173	17	12–13.5Gyx2	Mono	1% late GU Grade 3 toxicity
Hoskin (78)	197	37	8.5Gyx4	Mono	3–7% strictures
			9Gyx4		
			10.5Gyx3		
			13Gyx2		

GU = genitourinary; TUR = transurethral resection.

Original article

What is the ideal radiotherapy dose to treat prostate cancer? A meta-analysis of biologically equivalent dose escalation

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non-DE-CFRT; DE-CFRT; HFRT

HDR-BT mono and/or boost

Studies identified through database searching
(N = 201)

Studies after duplicates and updates
removed (N = 190)

Studies screened
(N = 190)

Studies excluded
(N = 124)

Full-text studies assessed for eligibility
(N = 66)

Updates of HFRT trials from national meetings (N = 1)
non-DE-CFRT to DE-CFRT (N = 4)
Full-text studies excluded, with reasons
retrospective, not a clinical trial, or non-randomized (31)
focus on stereotactic body radiation therapy or high dose rate brachytherapy (9)
report on dosimetry only (8)
report on efficacy or safety only (1)
Unacceptable definition for biochemical control (e.g. ASTRO with short FU time) (1)

Studies included in qualitative synthesis
• non-DE-CFRT to DE-CFRT (N = 7; n = 3,775)
• HFRT vs. non-DE-CFRT or DE-CFRT (N = 9; n = 1,828)

n = 5,385

Studies identified through database searching
(N = 270)

Studies after duplicates and updates
removed (N = 255)

Studies screened
(N = 255)

Studies excluded
(N = 123)

Studies assessed for eligibility
(N = 102)

Full-text studies excluded, with reasons
• focus on stereotactic body radiation therapy (6)
• report on dosimetry, physics only (12)
• report on acute outcomes / toxicity only (14)
• report not on primary or definitive HDR-BT (15)
• Unacceptable definition for biochemical control (e.g. ASTRO with short FU time) (16)

Studies included in qualitative synthesis
• HDR-BT mono (N = 7; n = 1,585)
• HDR-BT boost (N = 32; n = 5,786)

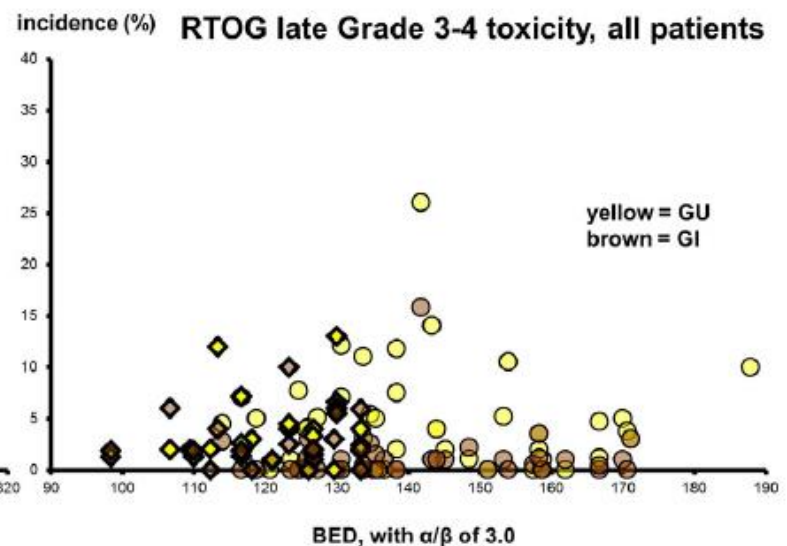
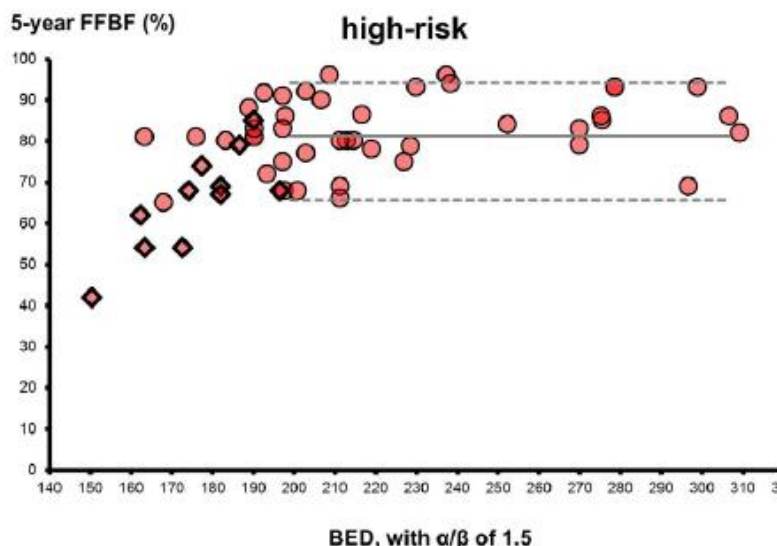
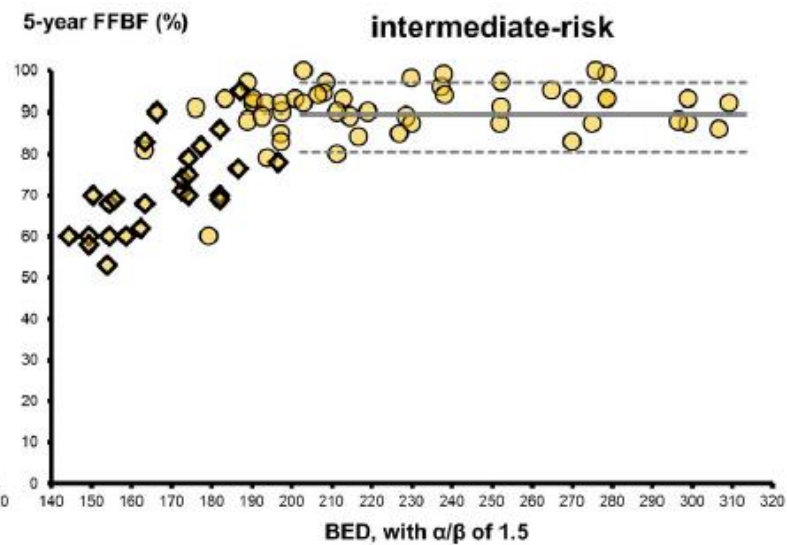
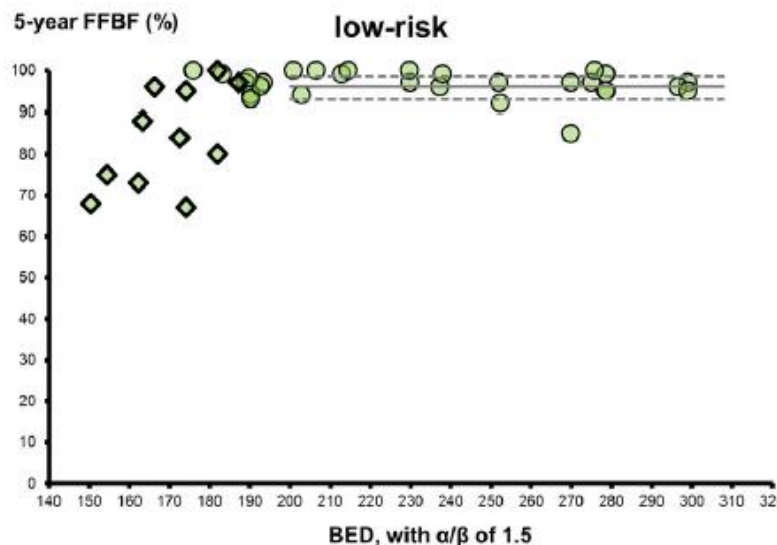
n = 7,371

Late RTOG grade 3–4 toxicity at BED range with α/β of 3.0

GU % range	Slope [‡]	GI % range	Slope [‡]
0–7	0.63	0–13	0.81
0–12	0.01	0–4	0.13

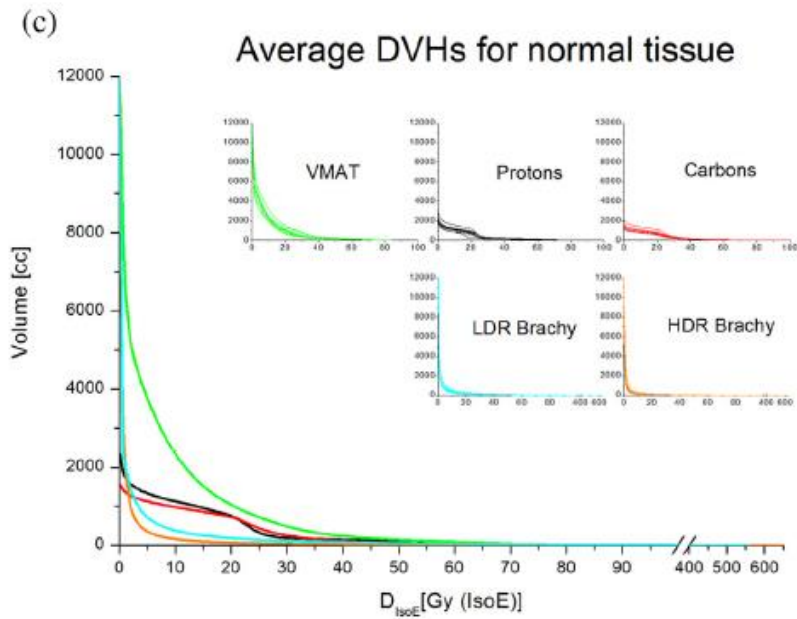
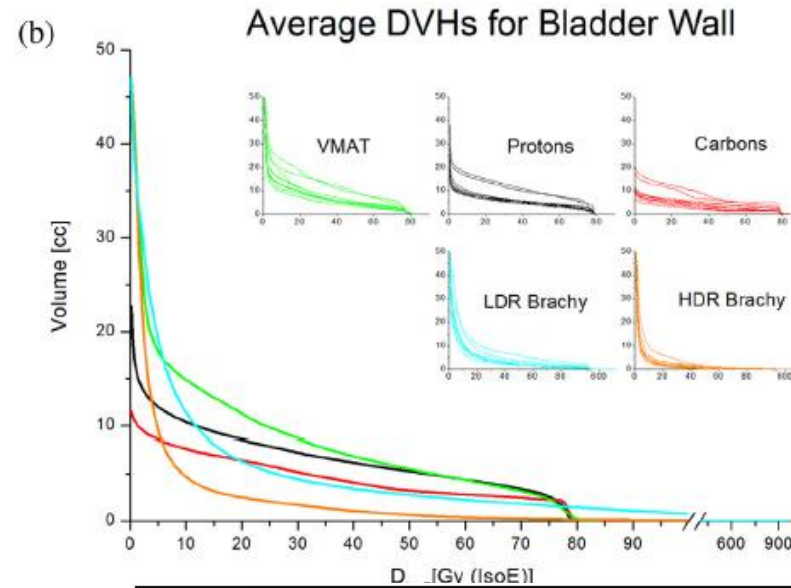
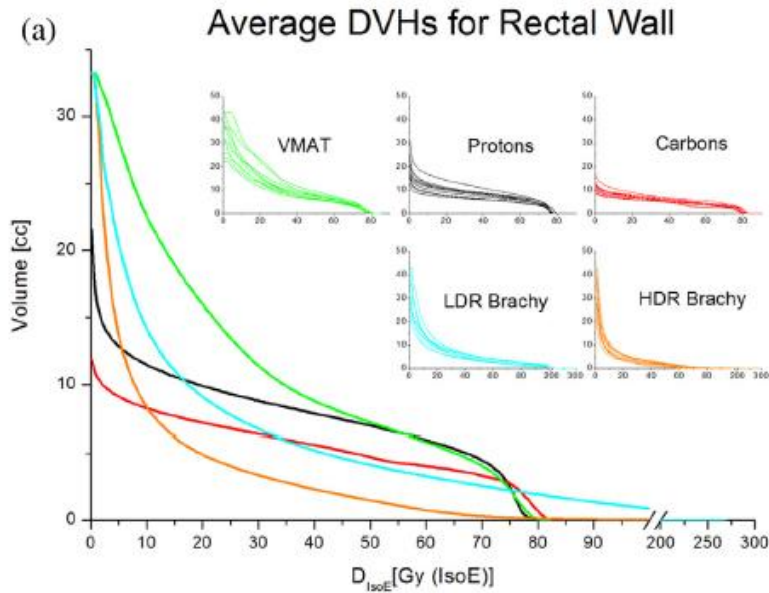
Non-DE-CFRT; DE-CFRT; HFRT

HDR-BT mono or boost



◆ non-DE-CFRT; DE-CFRT; HFRT

● HDR-BT mono and boost



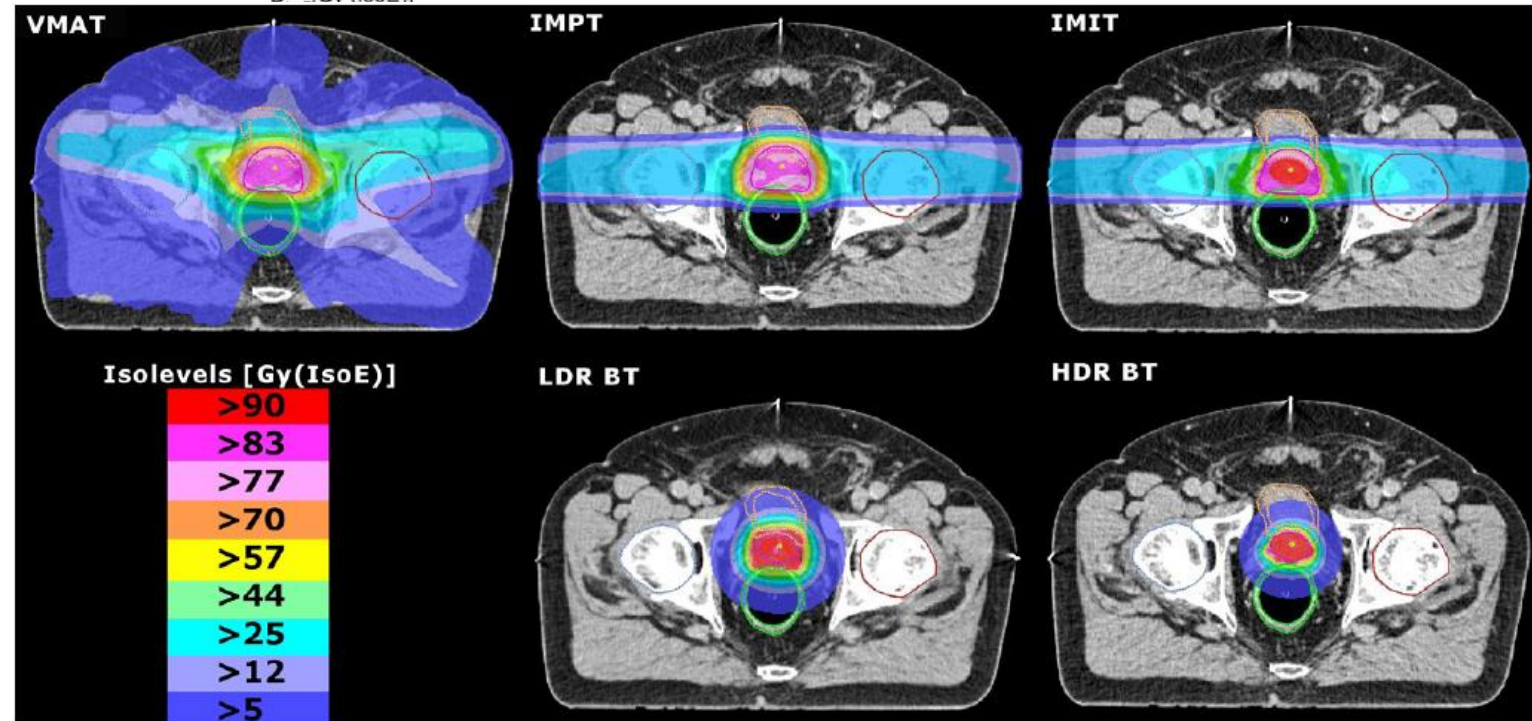
Physics Contribution

Dosimetric Considerations to Determine the Optimal Technique for Localized Prostate Cancer Among External Photon, Proton, or Carbon-Ion Therapy and High-Dose-Rate or Low-Dose-Rate Brachytherapy

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Standard leczenia raka prostaty pośredniej (niekorzystnej) i wysokiej grupy ryzyka w WCO

- 50 Gy (2Gy/fr) + BT HDR 1x15 Gy +/- HT

α/β [Gy]	1,5	Zakład Brachyterapii Wielkopolskiego Centrum Onkologii									
<u>Dawka na guz</u>	Prostata	Pacjent:									
EBRT 1		BED	EQD ₂		EBRT 2		BED	EQD ₂		Dawka całkowita EBRT	
		[Gy _{α/β}]	[Gy]				[Gy _{α/β}]	[Gy]			
liczba frakcji n	25				liczba frakcji n					BED	EQD ₂
dawka / frakcja d [Gy]	2	4,7	2,0		dawka / frakcja d [Gy]		0,0	0,0		[Gy _{α/β}]	[Gy]
TOTAL	50,0	116,7	50,0		Dawka całkowita	0,0	0,0	0,0		EBRT 1+2	116,7 50,0
HDR	D	BED	EQD ₂								
	[Gy]	[Gy _{α/β}]	[Gy]								
dawka frakcyjna 1 D ₁	15	165,0	70,7							Dawka całkowita EBRT + HDR	
dawka frakcyjna 2 D ₂		0,0	0,0							BED	EQD ₂
dawka frakcyjna 3 D ₃		0,0	0,0							[Gy _{α/β}]	[Gy]
dawka frakcyjna 4 D ₄		0,0	0,0								
dawka frakcyjna 5 D ₅		0,0	0,0								
dawka frakcyjna 6 D ₆		0,0	0,0								
Dawka całkowita		165,0	70,7							EBRT + HDR	281,7 120,7

Przeciwwskazania do BT



Brachytherapy 11 (2012) 20–32

BRACHYTHERAPY

American Brachytherapy Society consensus guidelines for high-dose-rate prostate brachytherapy

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Absolute contraindications

Absolute contraindications for HDR brachytherapy include the following conditions:

1. Preexisting rectal fistula,
2. Medically unsuited for anesthesia, and
3. No proof of malignancy.

Table 2

Patient selection criteria for a curative combined HDRBT and external beam treatment.

Inclusion criteria

Stages T1b–T3b

Any Gleason score

Any PSA level

Exclusion criteria

TURP within 3–6 months

Maximum urinary flow rate (Q_{max}) <10 ml/s

IPSS > 20

Pubic arch interference

Lithotomy position or anaesthesia not possible

Rectal fistula



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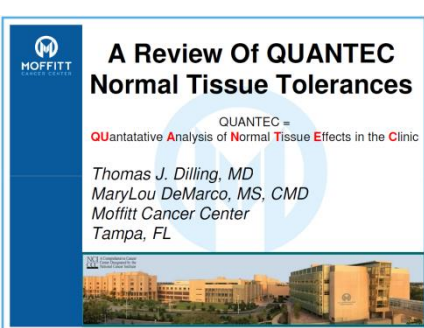


GEC/ESTRO recommendations

GEC/ESTRO recommendations on high dose rate afterloading brachytherapy for localised prostate cancer: An update

Peter J. Hoskin^{a,*}, Alessandro Colombo^{b,1}, Ann Henry^{c,1}, Peter Niehoff^{d,1}, Taran Paulsen Hellebust^{e,1},
Frank-Andre Siebert^{f,1}, Gyorgy Kovacs^{g,1}

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Ograniczenia dawek w OARs dla EBRT

- Rectum
- V50 < 50%, V60 < 35%, V65 < 25%,
- V70 < 20%, V75 < 15%
- Pęcherz
- V80 < 15%, V75 < 25%,
- V70 < 35%, V65 < 50%
- Opuszka prącia
- D70 < 70 Gy D90 < 50 Gy
- mean dose to 95% of volume to < 50 Gy
- głowy kk. udowych
- Dmax < 50 Gy
- V50 < 5%

American Journal of Clinical Oncology • Volume 34, Number 4, April 2011 Rectal Dose Constraints for IMRT of the Prostate

TABLE 5. Constraints in Use

	RTOG	UTHSCSA	Univ. Miami	Cedars Sinai	MSKCC	DFCI/BWH
Volume	Prostate only	Same for prostate with or without pelvis	Prostate + proximal SVs	Same for prostate with or without pelvis	Prostate + proximal half of SV	Same for prostate with or without pelvis
IMRT method	Any	Tomo, Varian or Rapid Arc	Rapid Arc	Rapid Arc or 7 field IMRT	In house	Sliding window (Varian Eclipse)
Total prescribed dose	73.8 Gy	77 Gy	80 Gy	77.7 Gy for int. risk at 1.85/d	86.4 Gy	75.6 Gy
How prescribed	Minimum dose (100%)	95% isodose	>95% PTV	100%	100% isodose-does not cover rectum/prostate overlap	99% of PTV receives 100% of prescribed dose
Allowable PTV inhomogeneity	+7%	±5%	Nominally 10% (up to 15%)	7%	110%	Max dose in PTV less than 110% of prescribed
How rectum defined (see key)	1	2	3	4	5	6
Rectum constraints						
85 Gy	—	—	—	—	85.5 max	83 Gy max
80 Gy	—	—	—	—	—	—
75 Gy	15%	5%	—	—	30% (V75.6)	—
70 Gy	25%	20%	—	25%	—	<10 mL
65 Gy	35%	—	17%–22%	—	—	—
60 Gy	50%	—	—	—	—	—
55 Gy	—	30%	—	—	—	—
50 Gy	—	—	—	50%	—	—
45 Gy	—	—	—	—	53% (V47)	<53% (V47)
40 Gy	—	50%	35%–40%	—	—	—
How bladder defined	Whole bladder	Whole bladder	Whole bladder	Whole bladder as low as reason-able	Whole bladder	Whole bladder
85 Gy	—	—	—	—	—	—
80 Gy	15%	—	—	—	—	—
75 Gy	25%	—	—	—	—	—
70 Gy	35%	25%	—	—	—	—
65 Gy	50%	—	25%	—	—	—
60 Gy	—	—	—	—	—	—
55 Gy	—	—	—	—	—	—
50 Gy	—	—	—	—	—	—
45 Gy	—	—	—	—	53% (V47)	53% (V47)
40 Gy	—	—	50%	—	—	—

The investigators emphasized that these are not absolute and represent goals and final determination is based on careful evaluation of the isodose pans and dose-volume histograms. If a range is given, the lower number is the target with allowance up to the higher. Rectal volume definitions are defined in the Appendix.

Ograniczenia dawek w OARs dla EBRT 50Gy podczas leczenia skojarzonego stosowanego w WCO

- Rectum i pęcherz $V50 < 50\%$
- głowy kk. udowych $D_{\max} < 50 \text{ Gy}$
- Opuszka prącia $D_{\text{mean}} < 35 \text{ Gy}$

Ograniczenia dawek w OARs dla BT HDR 15 Gy podczas leczenia skojarzonego stosowanego w WCO



GEC/ESTRO recommendations

GEC/ESTRO recommendations on high dose rate afterloading brachytherapy for localised prostate cancer: An update

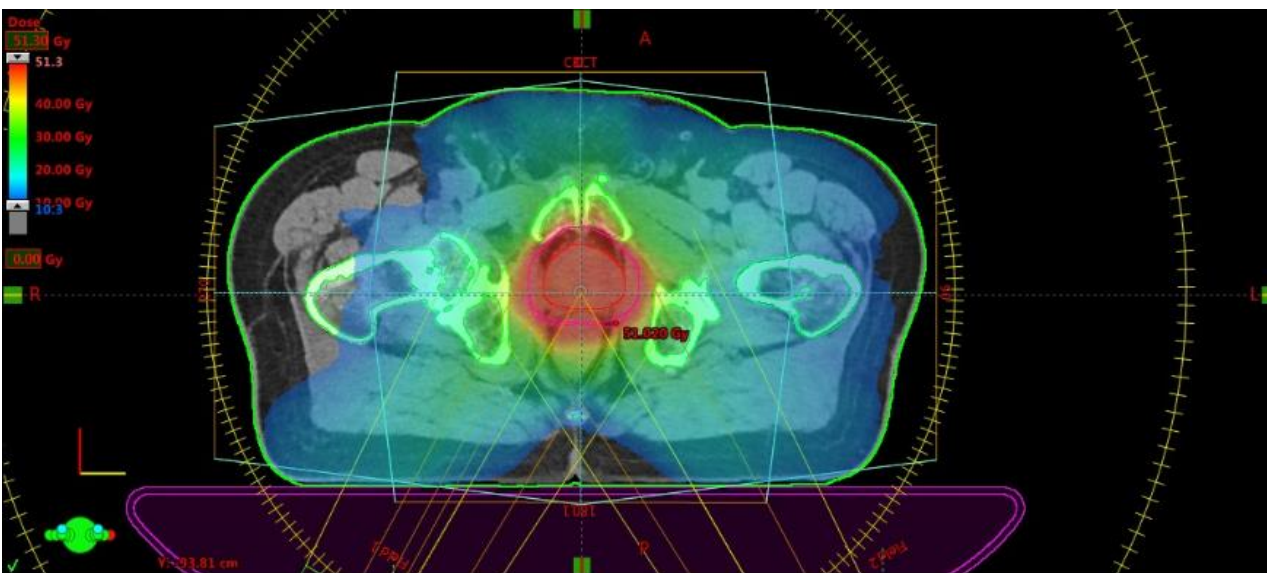
Peter J. Hoskin^{a,*}, Alessandro Colombo^{b,1}, Ann Henry^{c,1}, Peter Niehoff^{d,1}, Taran Paulsen Hellebust^{e,1}, Frank-Andre Siebert^{f,1}, Gyorgy Kovacs^{g,1}

^a Mount Vernon Cancer Centre, Northwood, UK; ^b Department of Radiotherapy, Manzoni Hospital, Lecco, Italy; ^c St. James Institute for Oncology, Leeds, UK; ^d Department of Radiotherapy, City Hospital Cologne, Germany; ^e DNR Norwegian Radium Hospital, Oslo, Norway; ^f Universitätsklinikum Schleswig-Holstein, Kiel; and ^g University Hospital Schleswig-Holstein Campus Lübeck, Germany

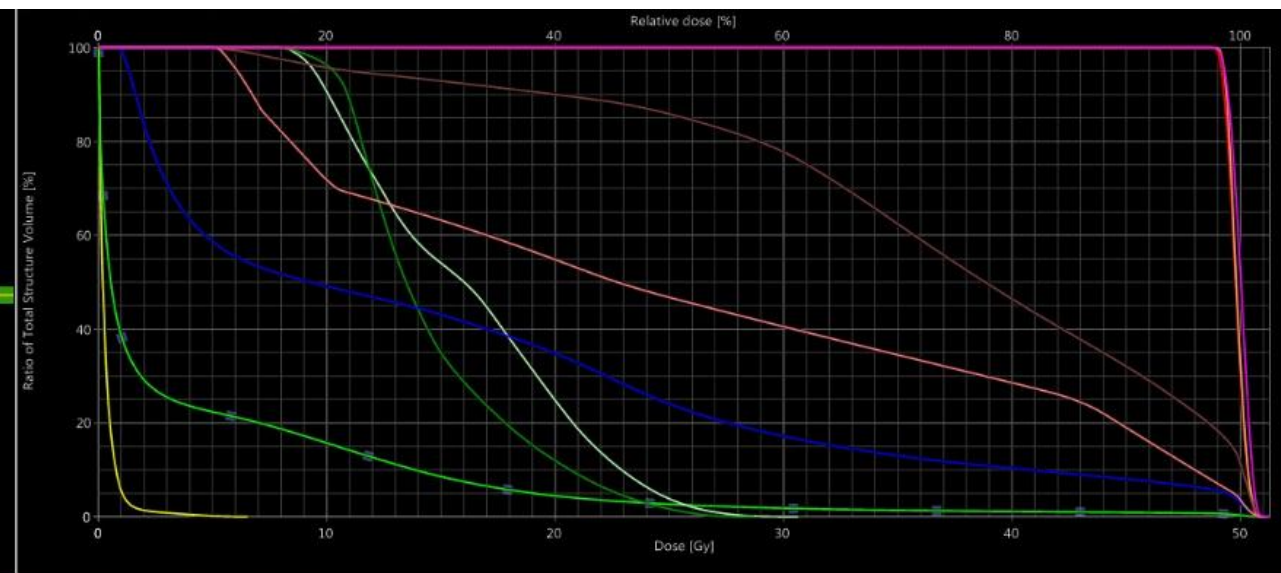
- Rectum: $D2\text{ cc} \leq 75\text{ Gy EQD}_2$
- Urethra:
 - o $D0.1\text{ cc} \leq 120\text{ Gy EQD}_2$
 - o $D10 \leq 120\text{ Gy EQD}_2$
 - o $D30 \leq 105\text{ Gy EQD}_2$

- Rectum ($\alpha/\beta=3$)
- $D2\text{cc} \leq 65\%$
- $D10 < 75\%$
- $D\text{max} < 100\%$
- Urethra ($\alpha/\beta=5$)
- $D0.1\text{cc i } D10 \leq 130\%$
- $D30 \leq 115\%$
- Pęcherz ($\alpha/\beta=5$)
- idealnie $D\text{max} < 100\%$
- $D10 < 75\%$

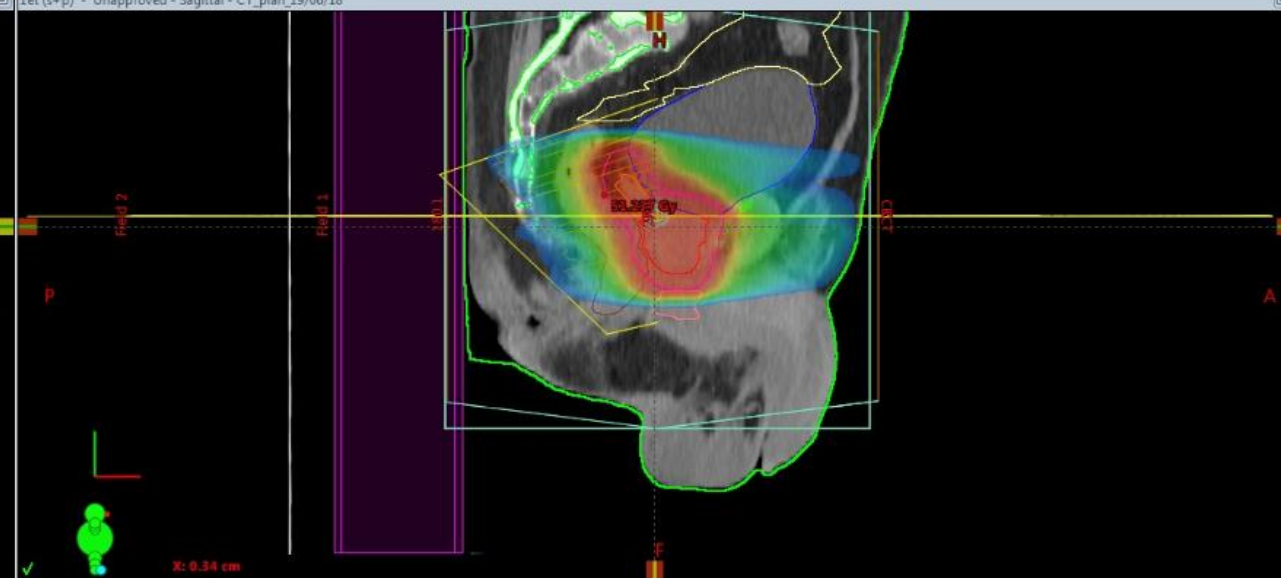
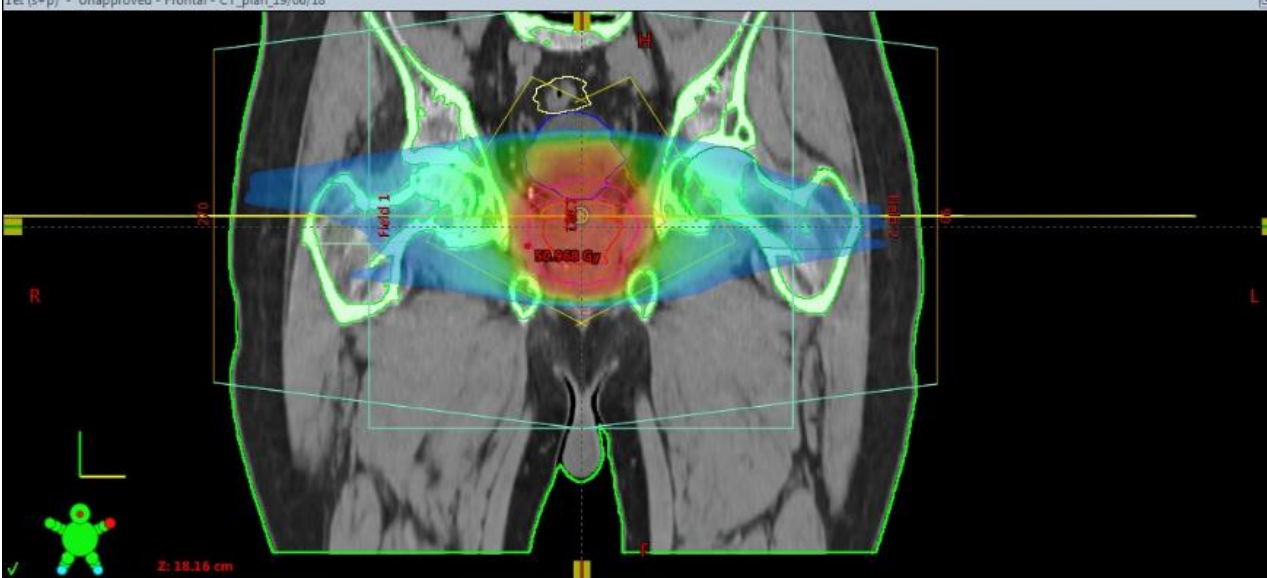
RA 50 Gy



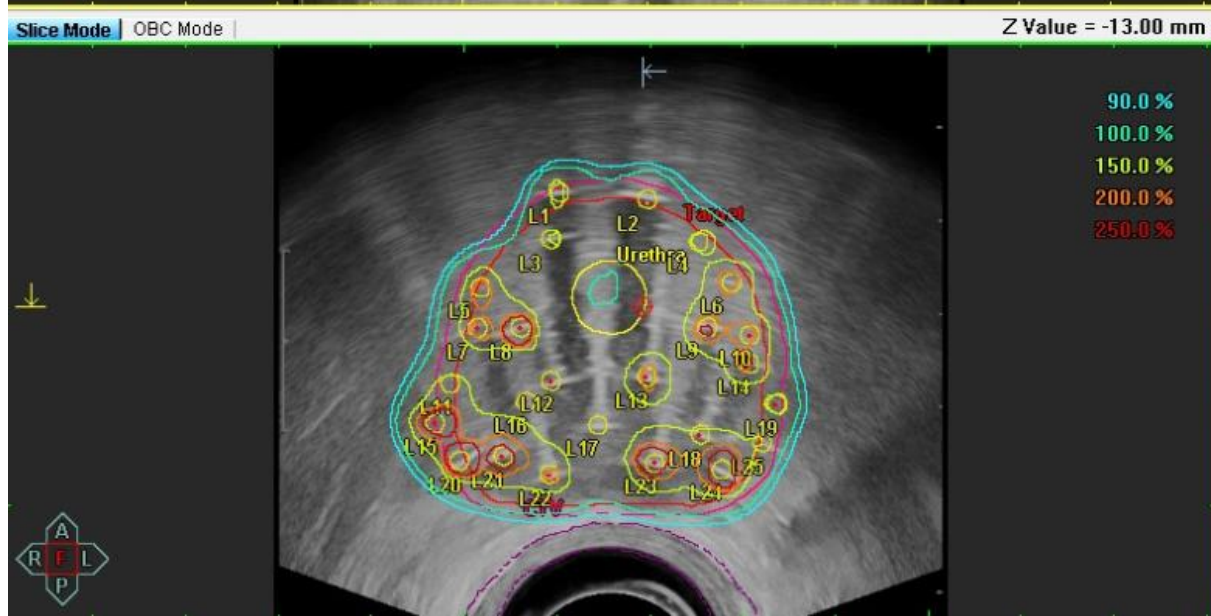
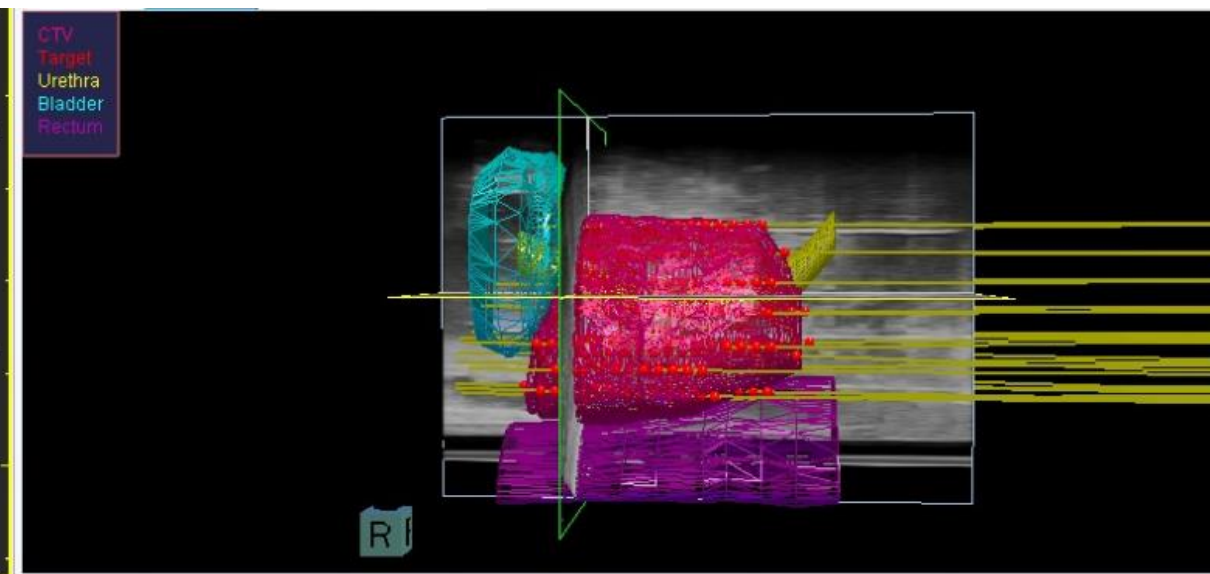
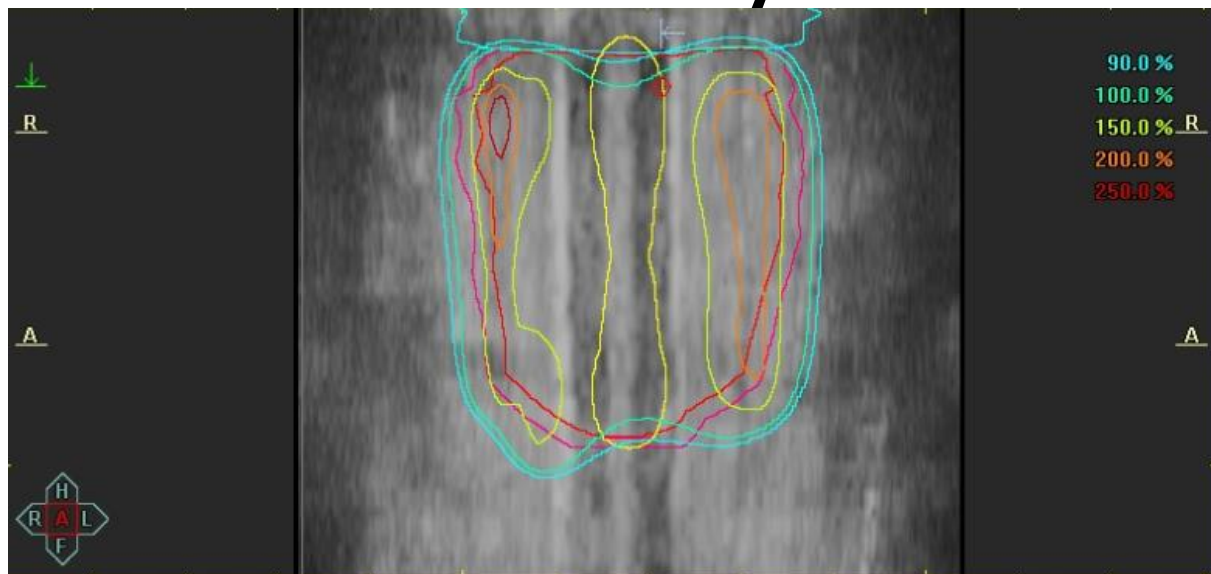
let (s+p) - Unapproved - Frontal - CT_plan_19/06/18



let (s+p) - Unapproved - Sagittal - CT_plan_19/06/18



BT HDR 15 Gy – Real time



RA 50 Gy + 15 Gy BT HDR (120,7 Gy EQD2)

- **Rectum**

- EBRT

V50 = 11,2%

- EBRT + BT

D2cc = 75Gy EQD2

Dmax = 98 Gy EQD2 (worst scenario)

Urethra

D0.1cc = 111,3 Gy EQD2

D10 = 108,6 Gy EQD2

D30 = 104,6 Gy EQD2

- **Pęcherz**

- EBRT

V50 = 3,6%

- EBRT + BT

D10 (D1,69cc) = 76,1 Gy EQD2

Dmax = 94,4 Gy EQD2 (worst scenario)

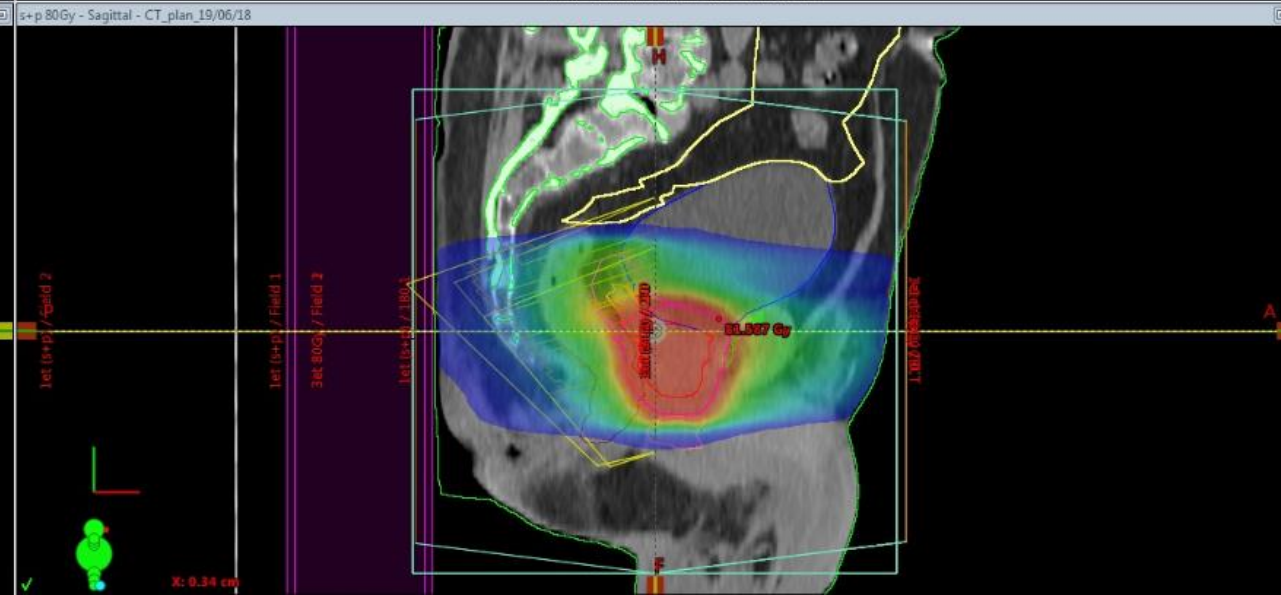
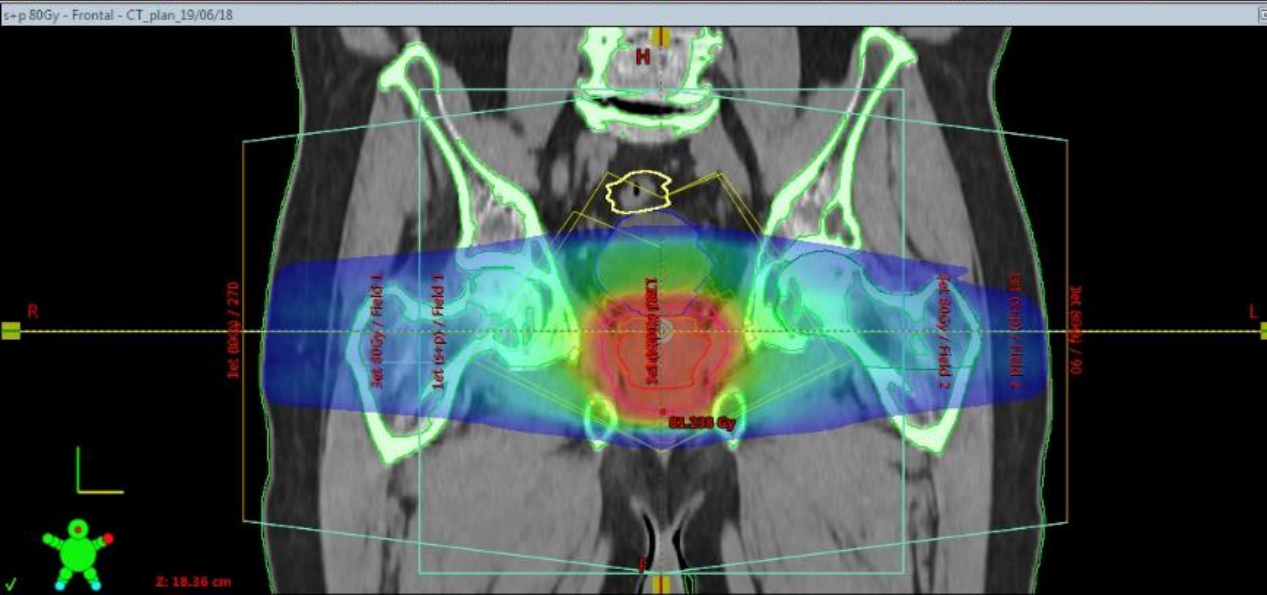
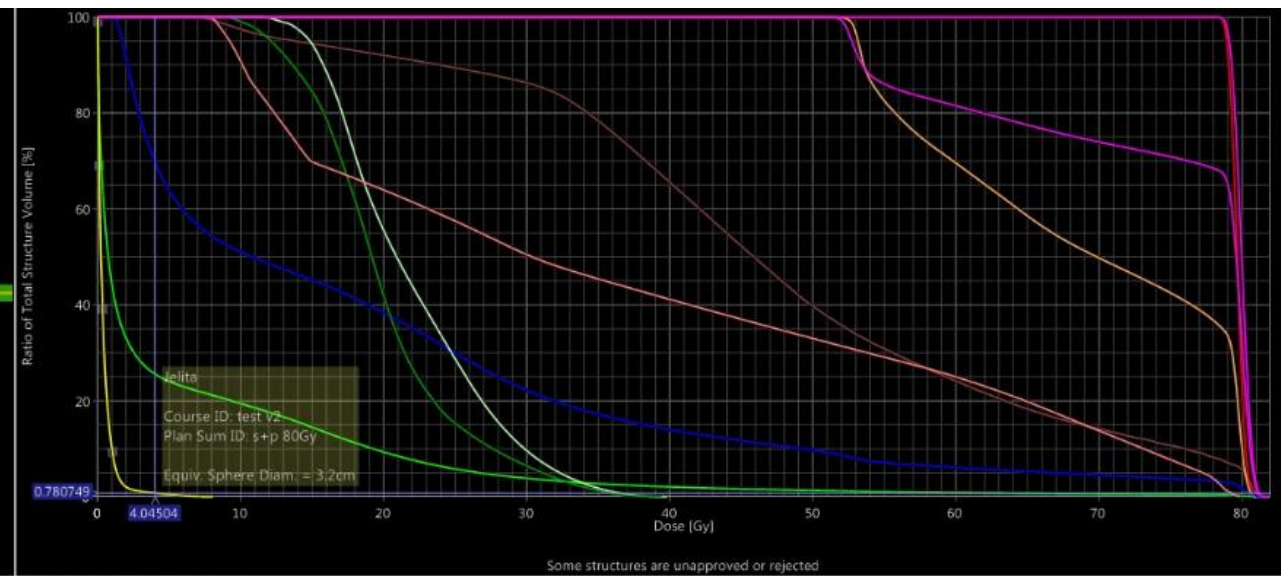
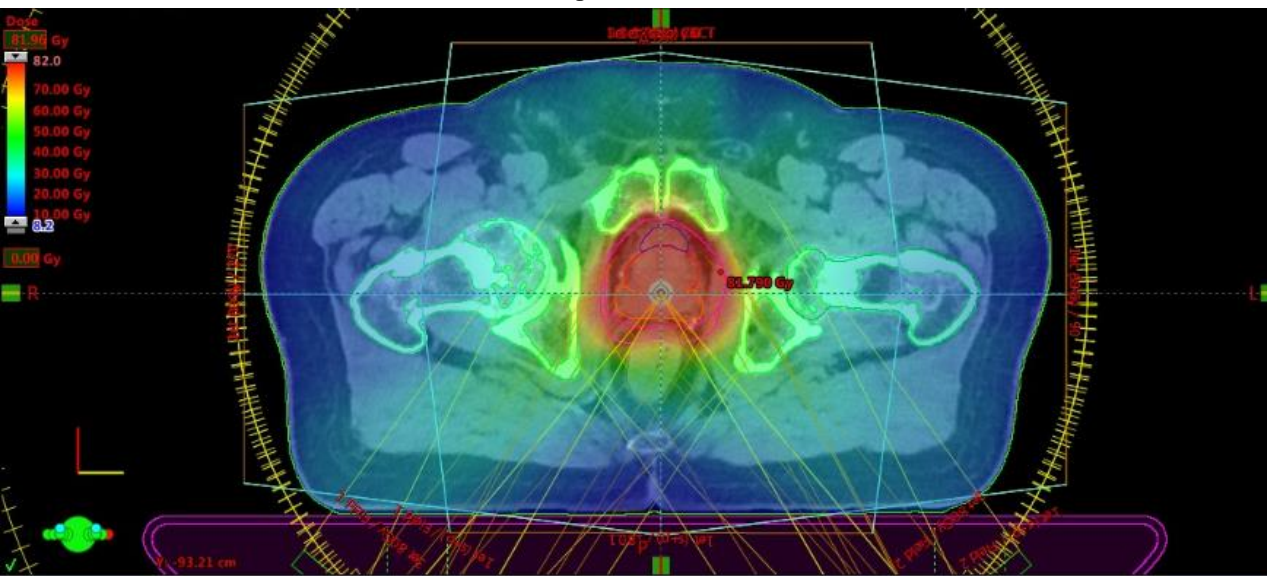
- **Opuszka prącia (EBRT)**

Dmean = 25,6 Gy

- **Gł. Kk. Udowych (EBRT)**

Dmax Pr = 30,7 Gy; Dmax L = 28,7 Gy

RA 80 Gy



RA 80 Gy

- **Rectum**

V50 = **39,7%**, V60 = 24%,
V65 = 18,3%, V70 = 14,2%,
V75 = 10,7%
D2cc = **80,5 Gy**
Dmax = 81,7 Gy

- **Urethra**

Wszystkie parametry ~ 80 Gy

- **Pęcherz**

V80 = 1,6%, V75 = 3,8%,
V70 = 4,5%, V65 = 5,3%
V50 = 9,7%
Dmax = **81,8 Gy**
D1,69cc = 80,7 Gy

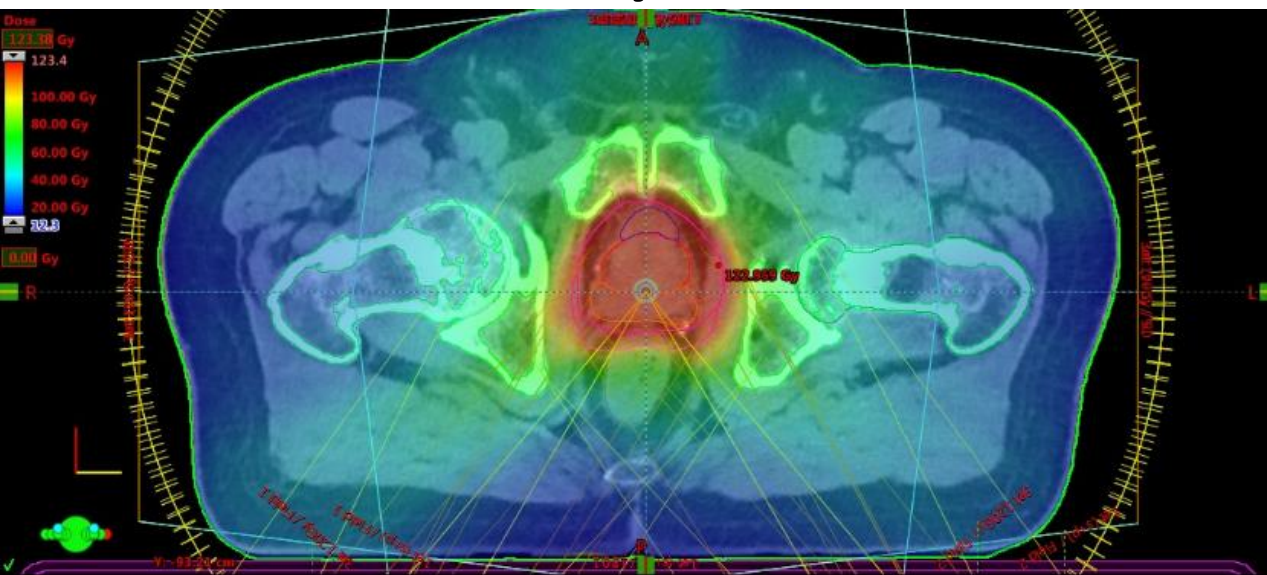
- **Opuszka prącia**

Dmean= 34,9 Gy

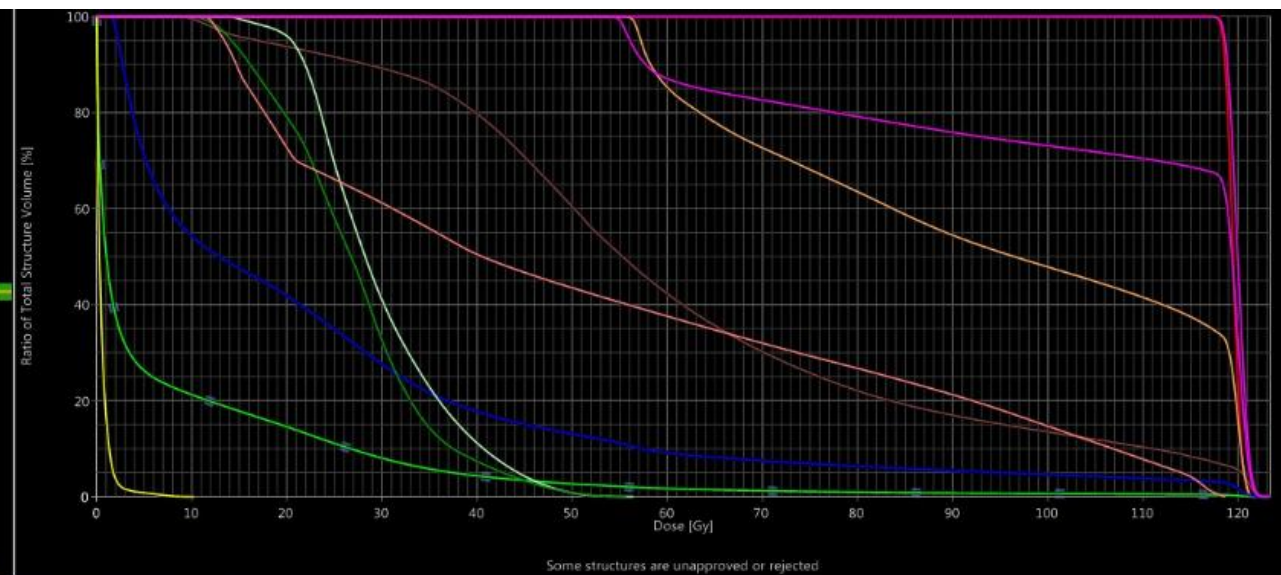
- **Gł. Kk. Udowych**

Dmax Pr = 39,8 Gy; Dmax L = 39,5 Gy

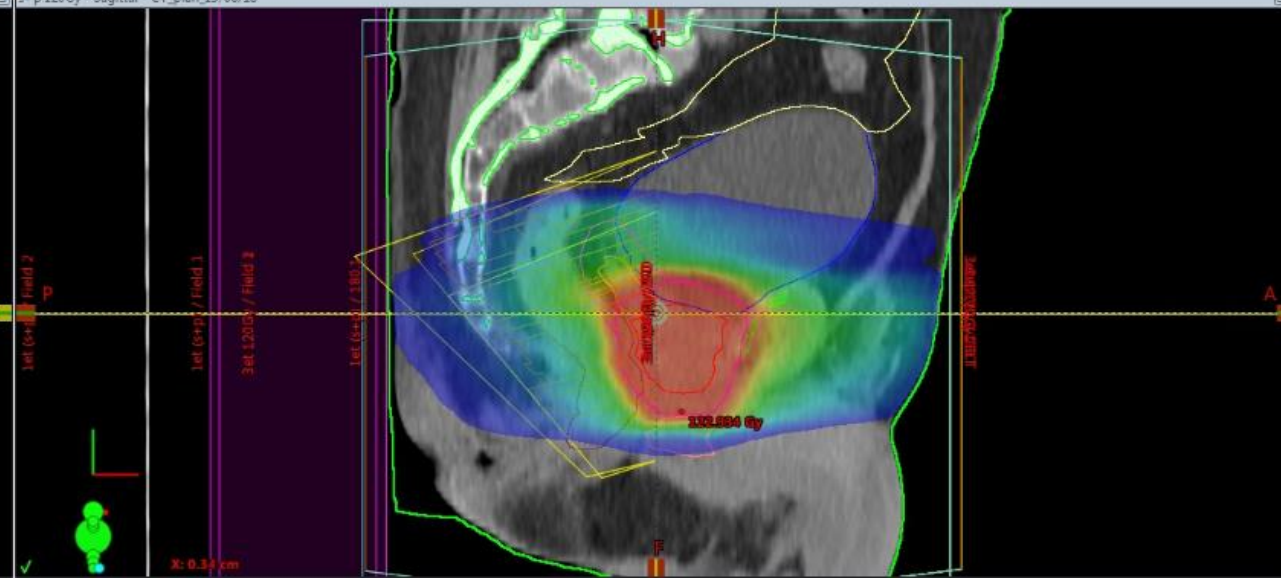
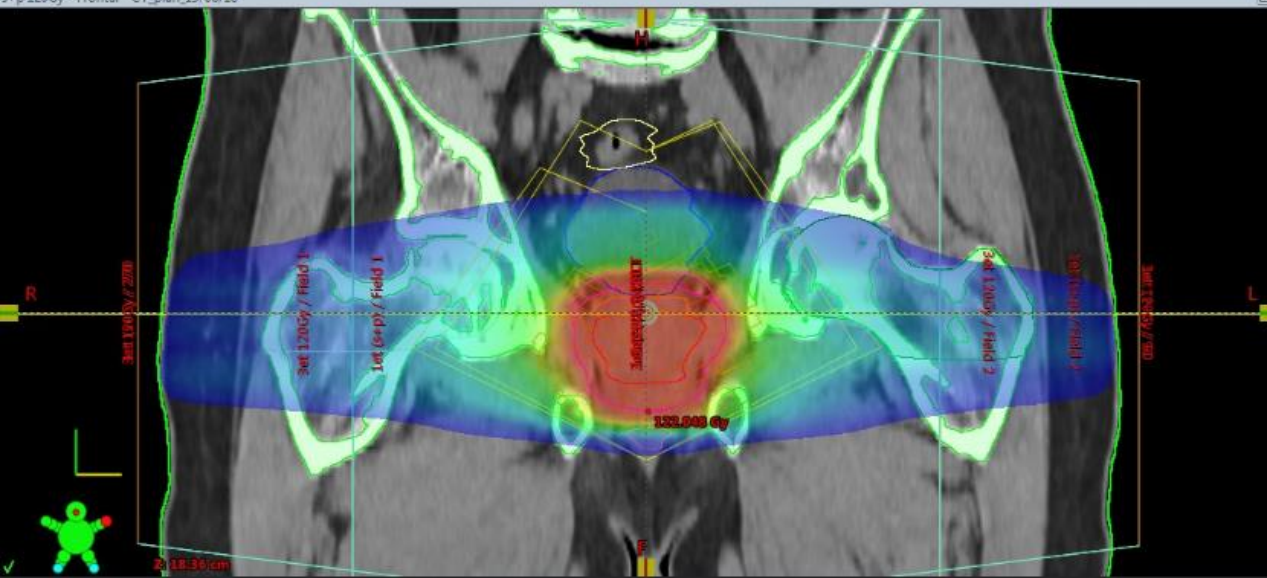
RA 120 Gy



s=p 120Gy - Frontal - CT_plan_19/06/18



s=p 120Gy - Sagittal - CT_plan_19/06/18



RA 120 Gy

- **Rectum**

V50 = 60,3%, V60 = 42,1%,

V65 = 35,6%, V70 = 30,2%,

V75 = 25,8%

D2cc = 121 Gy

Dmax = 123,1 Gy

- **Urethra**

Wszystkie parametry ~ 120 Gy

- **Pęcherz**

V80 = 6,8%, V75 = 7,6%,

V70 = 8,4%, V65 = 9,3%

V50 = 21,2%

Dmax = 122,9 Gy

D1,69cc = 121,1 Gy

- **Opuszka prącia**

Dmean= 53,4 Gy

- **Gł. Kk. Udowych**

Dmax Pr = 67,9 Gy; Dmax L = 72,6 Gy

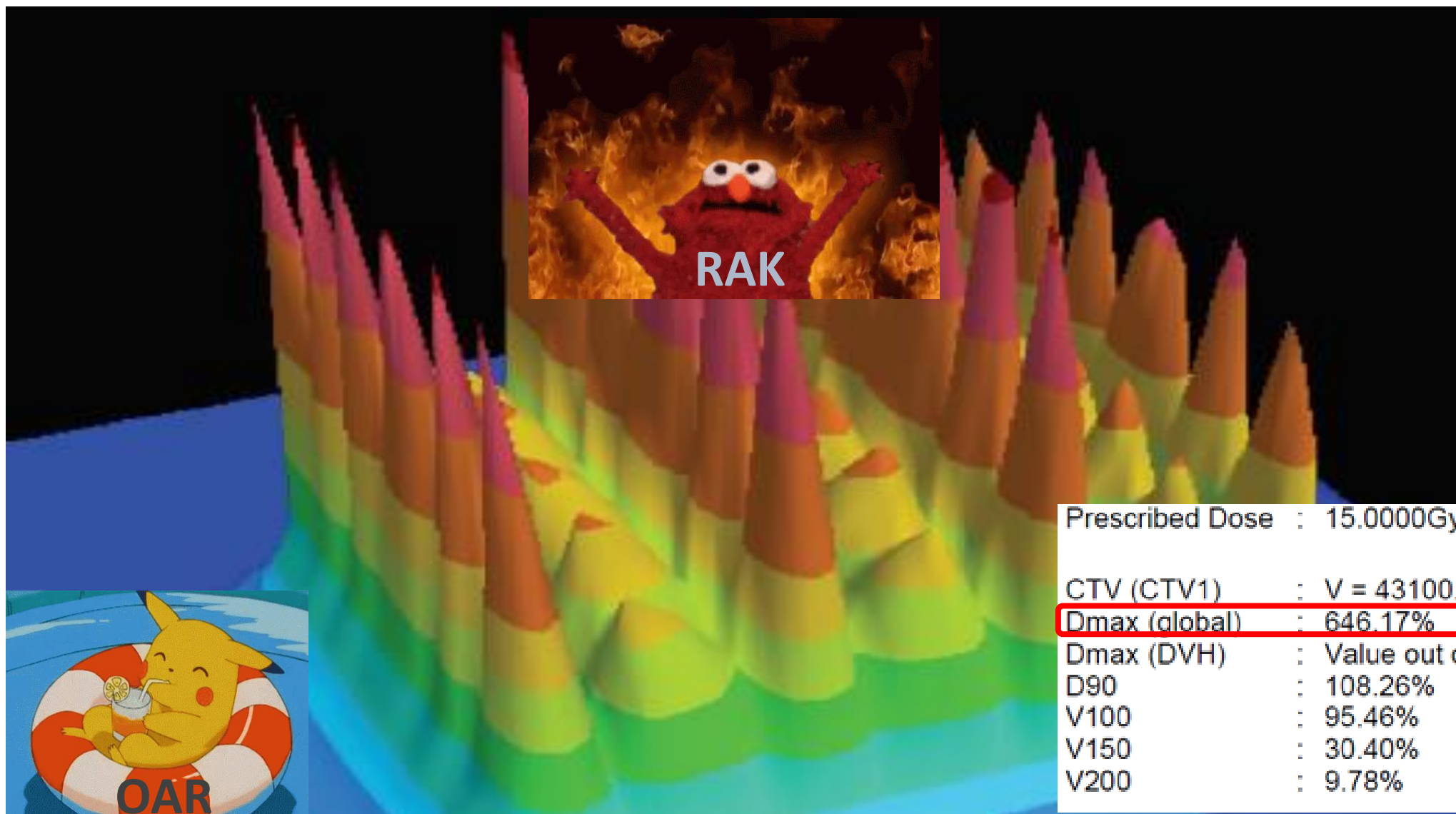
V50 Pr = 8,9%; V50 L = 5,6%

A photograph of a fashion runway show. A line of male models is walking towards the camera. They are all wearing dark sunglasses. The models are dressed in various styles of clothing, including sheer, lace-trimmed tops, a patterned scarf, and a dark jacket. The background is a simple, light-colored wall.

„Wszystkie modele są złe,
ale niektóre mogą być
przydatne”

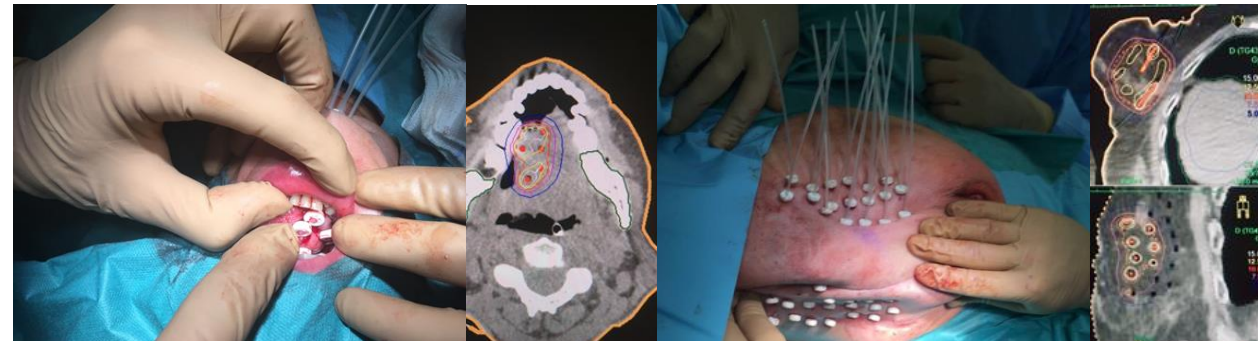
David R. Wigg

Efekt niehomogennego rozkładu dawki



Brachyterapia HDR jako boost pozwala na:

- Podanie wyższej biologicznie dawki na z CTV dużo większą dokładnością niż za pomocą jakiegokolwiek techniki EBRT
- Dobrą ochronę cewki, pęcherza moczowego i rectum dzięki możliwości optymalizacji dawki w trakcie planowania
- Znaczne obniżenie dawki deponowanej w tkankach miękkich i kościach (szpik)
- Skrócenie czasu leczenia
- Odciążenie aparatów EBRT
- Zwiększenie przychodu szpitala





Dziękuję za uwagę!