Rak stercza pośredniego i wysokiego ryzyka progresji; kiedy radioterapia, kiedy chirurgia?

Jacek Fijuth

Katedra Onkologii U.M.

Regionalny Ośrodek Onkologiczny

Łódź

3R, Łódź, 7-8.10.2017 r.

Rak stercza pośredniego (IR), wysokiego (HR) i bardzo wysokiego (vHR) ryzyka progresji (NCCN 2017)

pośrednie ryzyko progresji

T2b-T2c

Gl 3+4=7 (grupa gradingowa Gl 2), Gl 4+3=7 (grupa gradingowa Gl 3)

PSA 10-20 ng/ml

wysokie ryzyko progresji (HR)

T3a

Gl 8 (grupa gradingowa Gl 4)

Gl 9-10 (grupa gradingowa Gl 5)

PSA >20 ng/ml

bardzo wysokie ryzyko progresji (vHR)

T3b-4

grupa gradingowa Gl 5, w preparacie stopień 5

>4 rdzenie w biopsji Gl 8-10 (stopień 4 lub 5)

Nowa definicja grup 1-5 stopnia złośliwości według skali Gleason'a

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017 Staging Prostate Cancer

NCCN Guidelines Index
Table of Contents
Discussion

GLEASON GRADE GROUP DEFINITIONS

Gleason grade group 1: Gleason score ≤6
Only individual discrete well-formed glands

Gleason grade group 2: Gleason score 3+4=7
Predominantly well-formed glands with lesser component of poorly-formed/fused/cribriform glands

Gleason grade group 3: Gleason score 4+3=7
Predominantly poorly-formed/fused/cribriform glands with lesser component of well-formed glands*

IR

Gleason grade group 4: Gleason score 4+4=8; 3+5=8; 5+3=8
- **Only poorly-formed/fused/cribriform glands or**
- **Predominantly well-formed glands and lesser component lacking glands[1] or**
- **Predominantly lacking glands and lesser component of well-formed glands[1]**

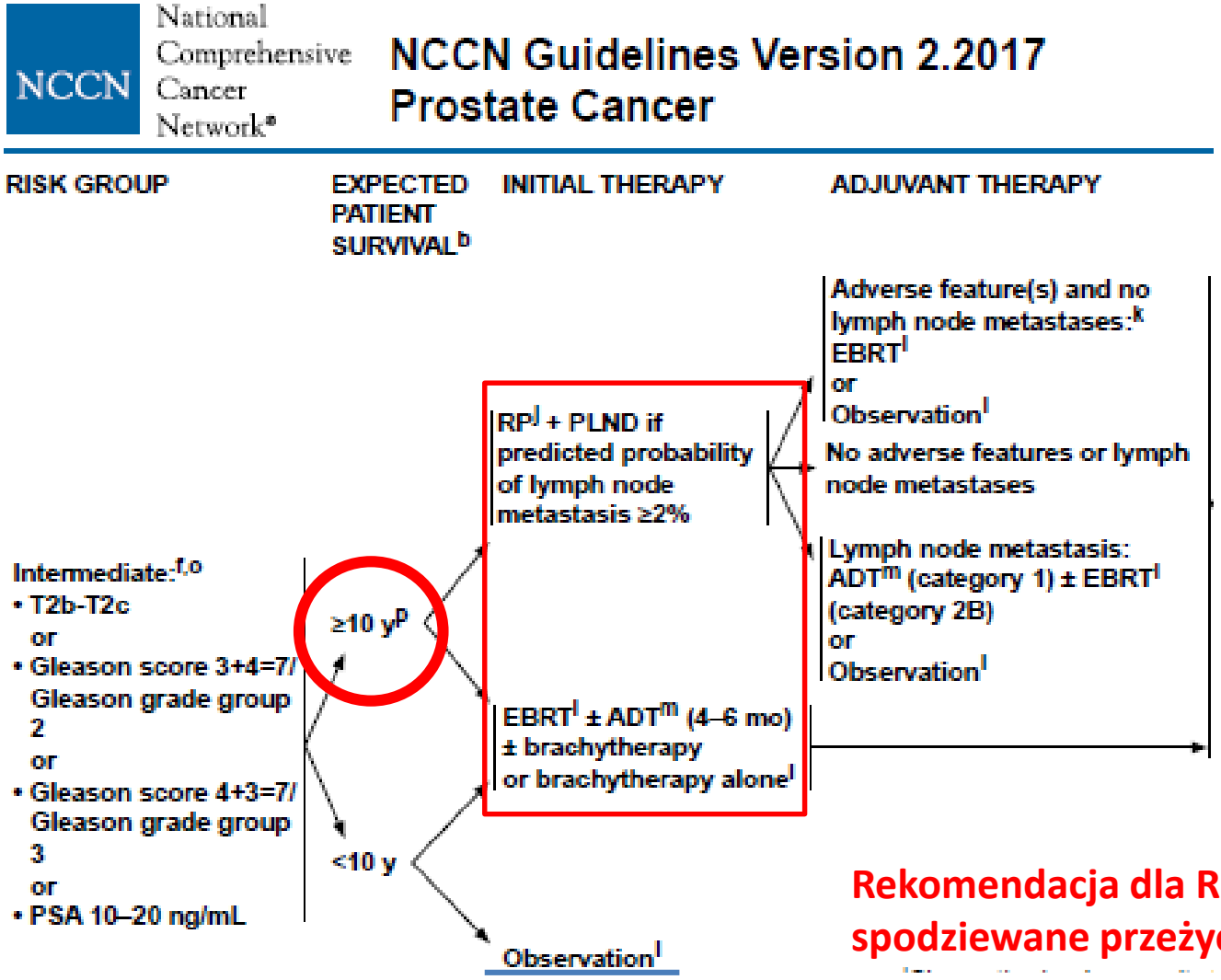
HR

Gleason grade group 5: Gleason score 9-10
Lack gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands[2]

vHR

RT PCa w grupie pośredniego ryzyka progresji (IR)

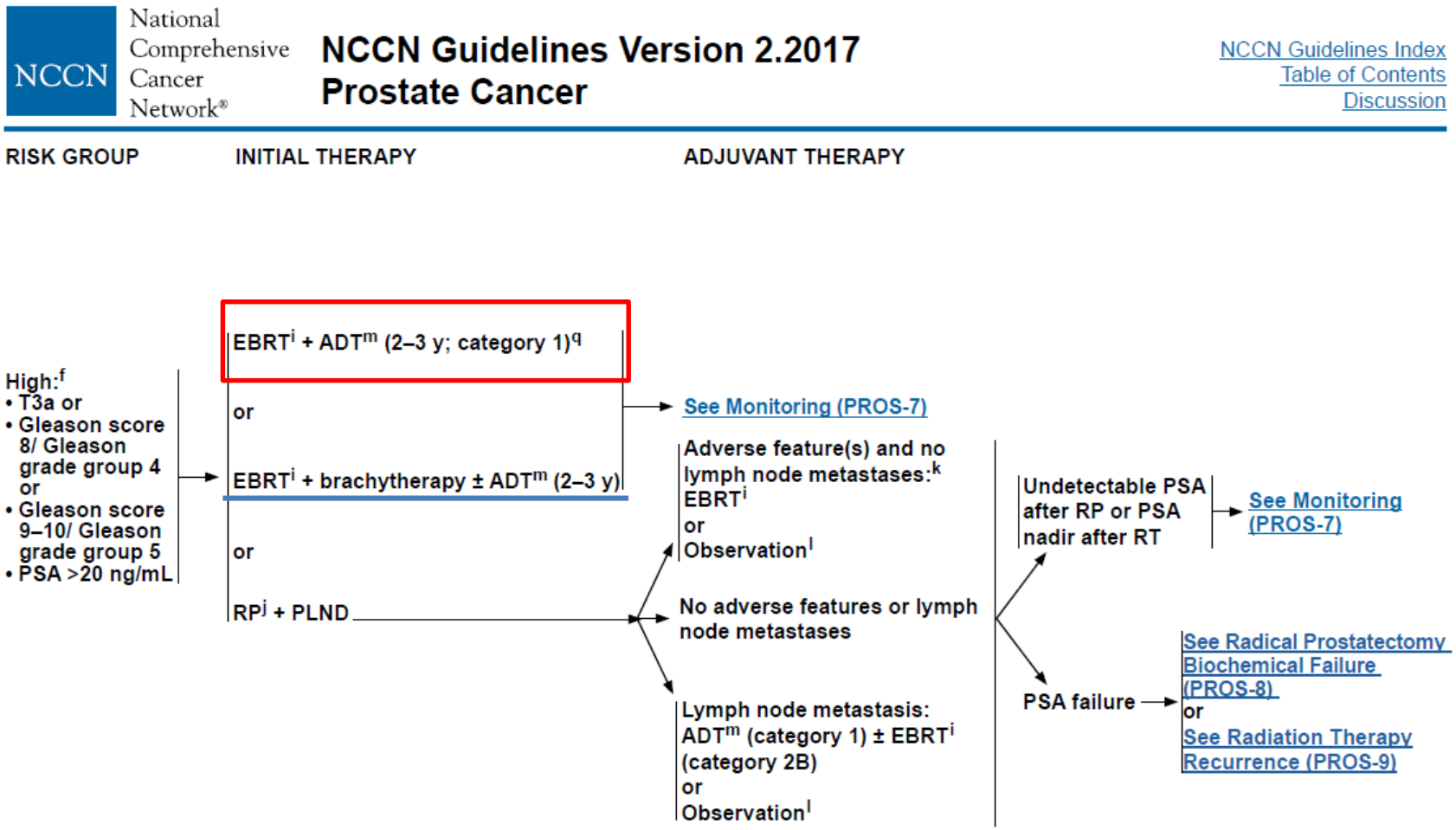
NCCN 2.2017



Rekomendacja dla RP gdy spodziewane przeżycie ≥10 lat!!!

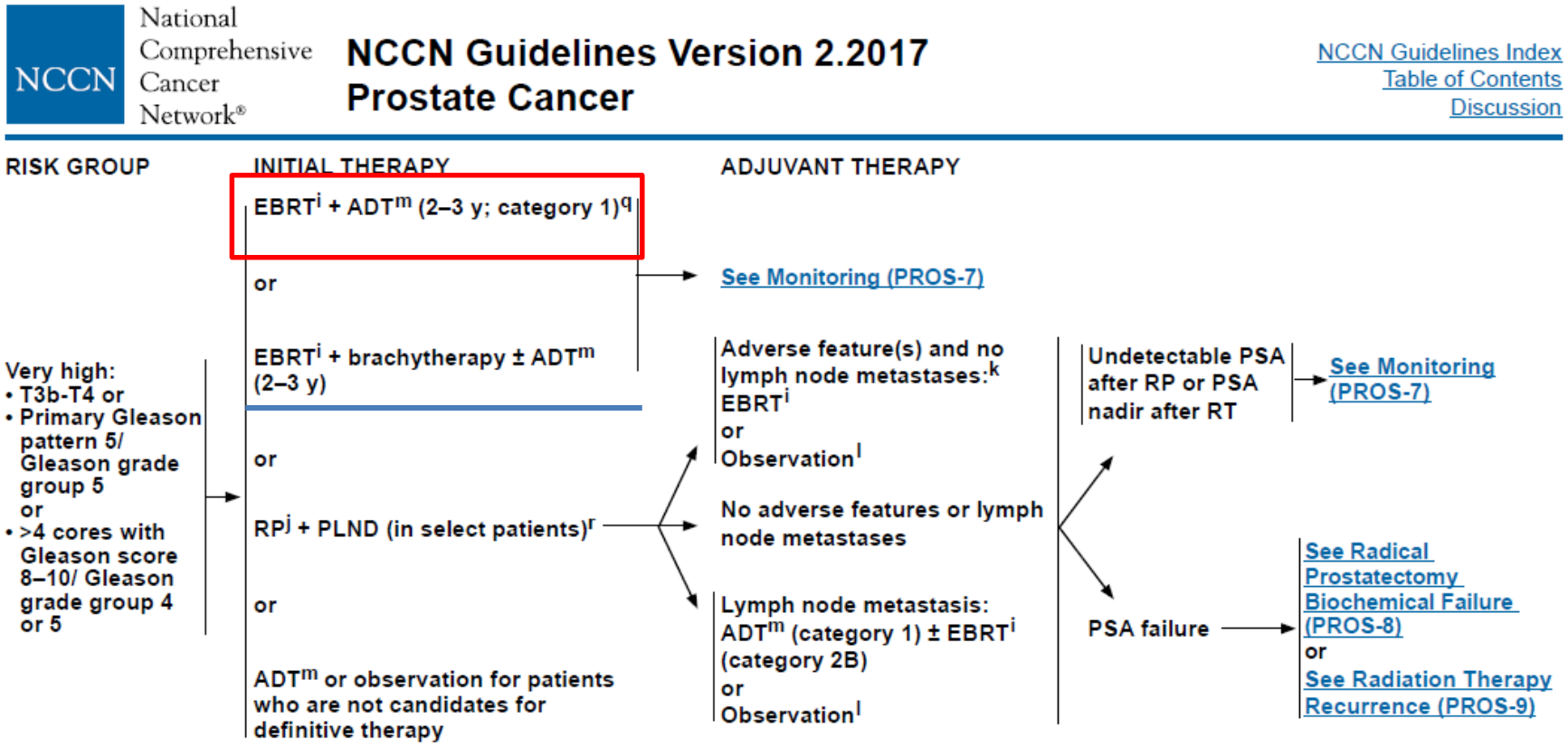
RT PCa w grupie wysokiego ryzyka progresji (HR)

NCCN 2.2017

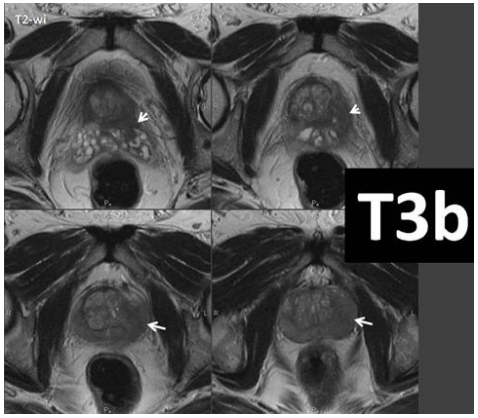


RT PCa w grupie bardzo wysokiego ryzyka progresji (vHR)

NCCN 2.2017



HR, vHR



Charakterystyka kliniczna:

- **zazwyczaj duża objętość guza (T2c, T3)**
- **przekraczanie granic anatomicznych (T3a, T3b)**
- **wysoki potencjał rozsiewu (i. Gleasona ≥8)**
- **wysoki potencjał istnienia subklinicznych przerzutów odległych (PSA >20 ng/ml)**

Skuteczne leczenie?

- **współdziałanie miejscowe (RT + ADT [*m.in. nasilenie apoptozy*])**
- **współdziałanie przestrzenne (ADT)**

ryzyko przerzutów odległych

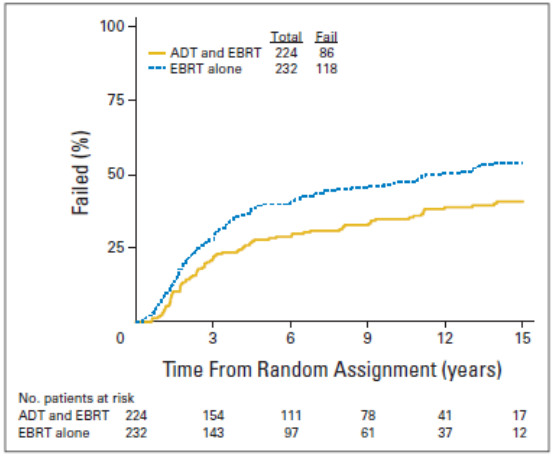


Fig 4. Time to distant metastasis. Failure is defined as disease beyond the pelvis by any method of evaluation. Time to distant metastasis is measured from the date of random assignment to the occurrence of an event or to the date of the most recent follow-up if no event occurred. ADT, androgen deprivation therapy; EBRT, external-beam radiotherapy.

VOLUME 26 · NUMBER 4 · FEBRUARY 1 2008
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Short-Term Neoadjuvant Androgen Deprivation Therapy and External-Beam Radiotherapy for Locally Advanced Prostate Cancer: Long-Term Results of RTOG 8610

Mack Roach III, Kyounghwa Bae, Joycelyn Speight, Harvey B. Wolkov, Phillip Rubin, R. Jeffrey Lee, Colleen Lawton, Richard Valicenti, David Grignon, and Miljenko V. Pilepich

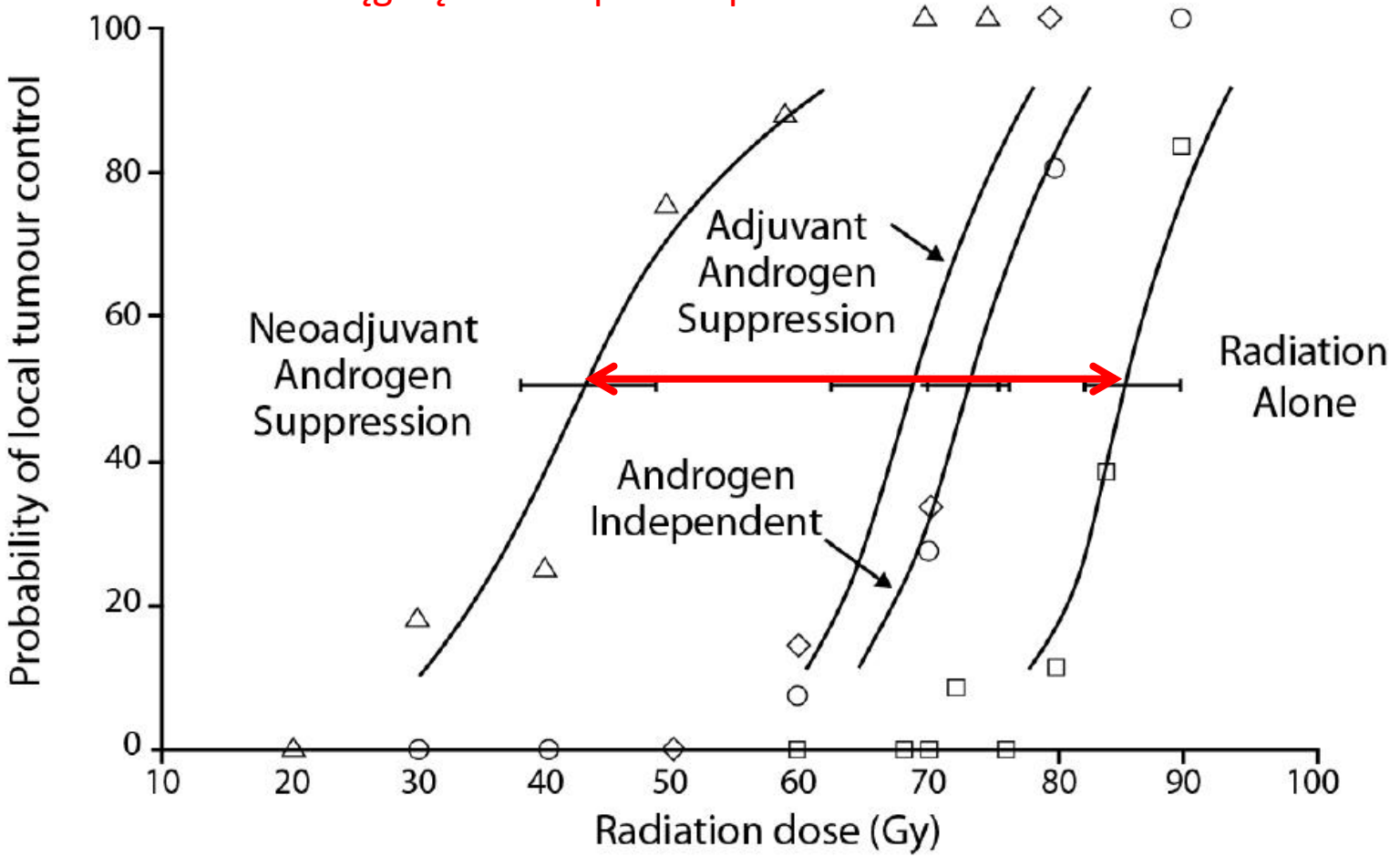
Radiotherapy and androgen deprivation therapy

- Adjuvant / Post-RT hormones:
  - DNA synthesis inhibition, cytoreduction, downsizing
  - need to eradicate fewer clonogens
  - volume reduction = decreasing hypoxic fraction
  - "additive" interaction (apoptosis)
- Neo-adjuvant / Pre-RT hormones:
  - DNA synthesis inhibition, cytoreduction, downsizing
  - need to eradicate fewer clonogens
  - volume reduction = decreasing hypoxic fraction
  - "supra-additive" interaction (apoptosis)

Fuks Z Isr J Med Sci 1995;31:76-85; Steel: Basic Clinical Radiobiology, Ed by Gordon Steel, Arnold Ed;
Zietman AL et al. IJROBP 1997;38:1067-70; Laverdière J et al. IJROBP 1997;37:247-52

Response to radiation +/- androgen deprivation of Shionogi tumours

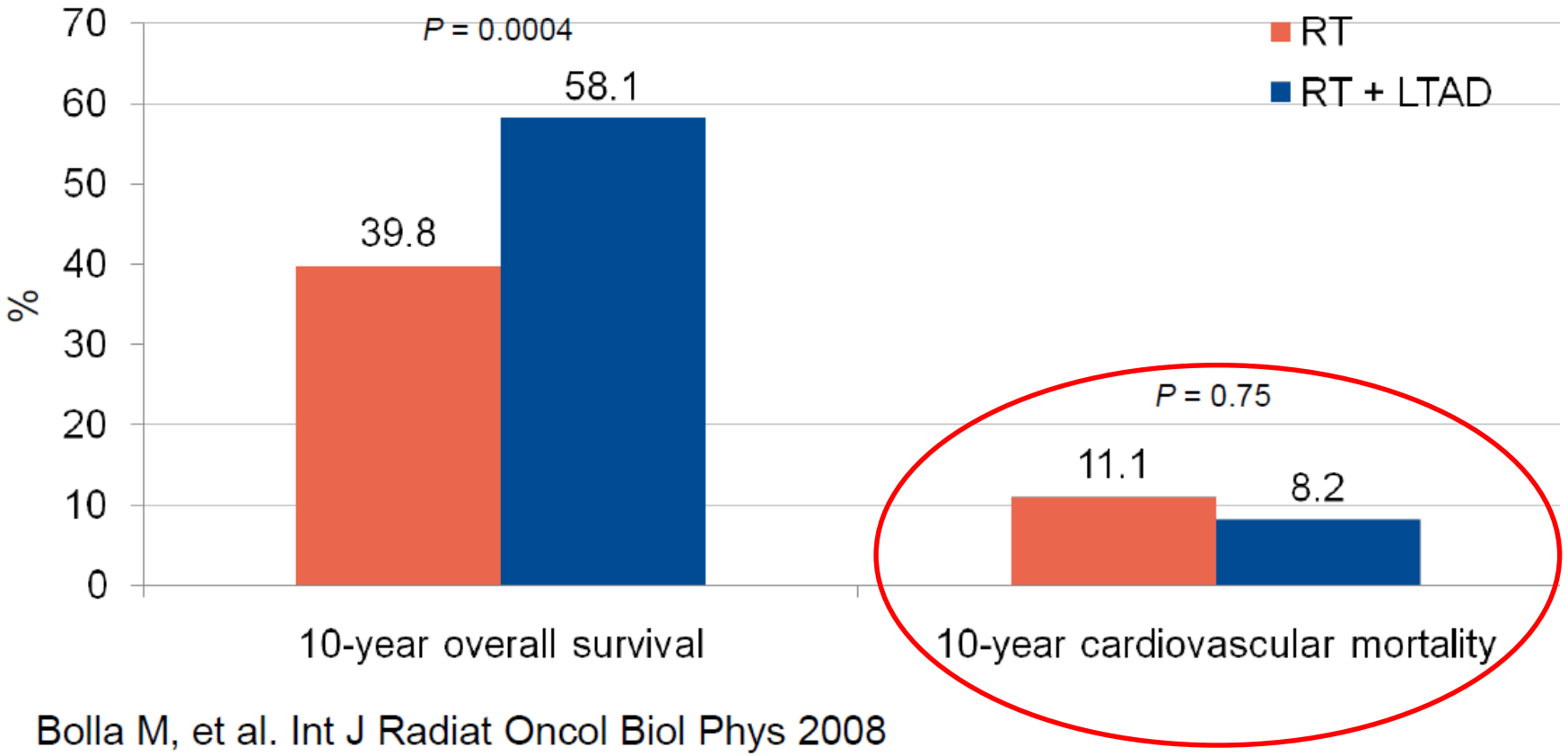
Zastosowanie neoadjuwantowej HT zmniejsza o 50% dawkę RT wymaganą do osiągnięcia 50% prawdopodobieństwa LC



Zietman AL, et al . Int J Radiat Oncol Biol Phys 1997

Long-term adjuvant HT to RT improved overall survival without increasing cardiovascular toxicity over RT alone

- Phase III EORTC 22861 trial: 415 patients with locally advanced PCa treated with RT alone or RT + long-term androgen deprivation (LTAD) (3 years); median FU: 9.1 years



Bolla M, et al. Int J Radiat Oncol Biol Phys 2008

59 Kongres ASTRO 2017 – SAN DIEGO

Kanon radykalnej RT w raku stercza (2017)

<u>Zależność dawka-efekt</u>

Zalecane dawki:

- >80 Gy w grupie pośredniego i wysokiego/b. wysokiego ryzyka progresji

- zwiększenie BED (dawki równoważnej biologicznie)
  → hipofrakcjonowanie
  → łączenie z BT

The Journal of Urology
Volume 195, Issue 5, May 2016, Pages 1453–1458

2016

Adult Urology

Survival Outcomes of Dose-Escalated External Beam Radiotherapy versus Combined Brachytherapy for Intermediate and High Risk Prostate Cancer Using the National Cancer Data Base

Arya Amini, Bernard Jones, Matthew W. Jackson, Norman Yeh, Timothy V. Waxweiler, Paul Maroni, Brian D. Kavanagh, David Raben

20,279 chorych IR (12,617) i HR z bazy NCDB (National Cancer Data Base)

Podwyższenie dawki EBRT + BT zmniejsza ryzyko zgonu

75.6 vs 81 Gy

Conclusion

Compared to EBRT (75.6 to 81 Gy) we observed an association of EBRT plus brachytherapy with a decreased risk of death in men with intermediate and high risk prostate cancer.

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Systematic review

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

Nicholas G. Zaorsky [a,b,*], Joshua D. Palmer [b], Mark D. Hurwitz [b], Scott W. Keith [c], Adam P. Dicker [b], Robert B. Den [b]

[a] Department of Radiation Oncology, Fox Chase Cancer Center; [b] Department of Radiation Oncology, Sidney Kimmel Cancer Center at Sidney Kimmel Medical College at Thomas Jefferson University; and [c] Department of Pharmacology and Experimental Therapeutics, Division of Biostatistics, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA, USA

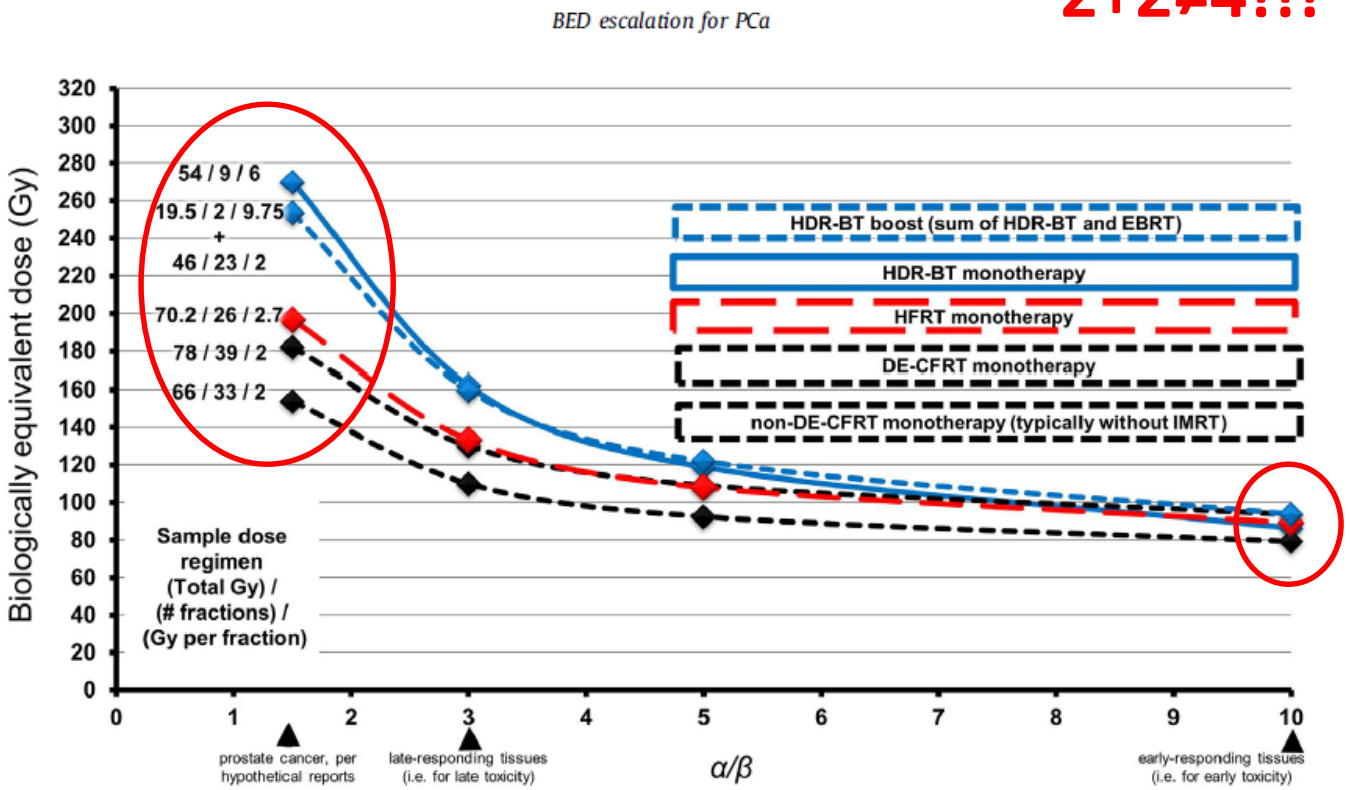
2016

Unikalna cecha PCa – α/β = 1,5

- hipofrakcjonowanie = ↗ d. frakcyjnej
- boost HDR

↗ ↗ ↗ dawki równoważnej biologicznie

2+2≠4!!!



Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Systematic review

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

Nicholas G. Zaorsky [a,b,*], Joshua D. Palmer [b], Mark D. Hurwitz [b], Scott W. Keith [c], Adam P. Dicker [b], Robert B. Den [b]

[a] Department of Radiation Oncology, Fox Chase Cancer Center; [b] Department of Radiation Oncology, Sidney Kimmel Cancer Center at Sidney Kimmel Medical College at Thomas Jefferson University; and [c] Department of Pharmacology and Experimental Therapeutics, Division of Biostatistics, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA, USA

PCa – α/β = 1,5

↗BED do 200-300Gy

IMRT/IGRT
Ochrona tkanek prawidłowych

Outcomes and toxicities of increasing BED for prostate cancer radiotherapy.

Study type	*N* (*n*)	BED (Gy) ranges at α/β		Risk group	5-year FFBFs at BED range with α/β of 1.5		Late RTOG grade 3–4 toxicity at BED range with α/β of 3.0			
		1.5	3.0		% Range	Slope‡	GU % range	Slope‡	GI % range	Slope‡
Non-DE-CFRT; DE-CFRT; HFRT		140–200	98–133	L I H	75–100 60–100 55–85	† 5.54* †	0–7	0.63	0–13	0.81
HDR-BT mono or boost		180–310	107–188	L I H	90–100 85–100 50–85	−0.11 0.31 0.42	0–12	0.01	0–4	0.13

Abbreviations: BED: biologically equivalent dose; BT: brachytherapy; CFRT: conventionally fractionated radiation therapy; DE: dose-escalated; FFBF: freedom from biochemical failure; GI: gastrointestinal; GU: genitourinary; HDR: high dose rate; HFRT: hypofractionated radiation therapy; H: high-risk; I: intermediate-risk; L: low-risk; *N*: studies; *n*: patients; RTOG: Radiation Therapy Oncology Group

Wzrost odsetka 5-letniego przeżycia bez wznowy biochemicznej w HR CaP

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Systematic review

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

Nicholas G. Zaorsky [a,b,*], Joshua D. Palmer [b], Mark D. Hurwitz [b], Scott W. Keith [c], Adam P. Dicker [b], Robert B. Den [b]

[a] Department of Radiation Oncology, Fox Chase Cancer Center; [b] Department of Radiation Oncology, Sidney Kimmel Cancer Center at Sidney Kimmel Medical College at Thomas Jefferson University; and [c] Department of Pharmacology and Experimental Therapeutics, Division of Biostatistics, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA, USA

Unikalna cecha PCa – α/β = 1,5

↗BED do 200-300Gy

IMRT/IGRT
Ochrona tkanek prawidłowych

Outcomes and toxicities of increasing BED for prostate cancer radiotherapy.

Study type	*N* (*n*)	BED (Gy) ranges at α/β		Risk group	5-year FFBFs at BED range with α/β of 1.5		Late RTOG grade 3–4 toxicity at BED range with α/β of 3.0			
		1.5	3.0		% Range	Slope‡	GU % range	Slope‡	GI % range	Slope‡
Non-DE-CFRT; DE-CFRT; HFRT		140–200	98–133	L	75–100	†	0–7	0.63	0–13	0.81
				I	60–100	5.54*				
				H	55–85	†				
HDR-BT mono or boost		180–310	107–188	L	90–100	−0.11	0–12	0.01	0–4	0.13
				I	85–100	0.31				
				H	50–85	0.42				

Abbreviations: BED: biologically equivalent dose; BT: brachytherapy; CFRT: conventionally fractionated radiation therapy; DE: dose-escalated; FFBF: freedom from biochemical failure; GI: gastrointestinal; GU: genitourinary; HDR: high dose rate; HFRT: hypofractionated radiation therapy; H: high-risk; I: intermediate-risk; L: low-risk; *N*: studies; *n*: patients; RTOG: Radiation Therapy Oncology Group

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Systematic review

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

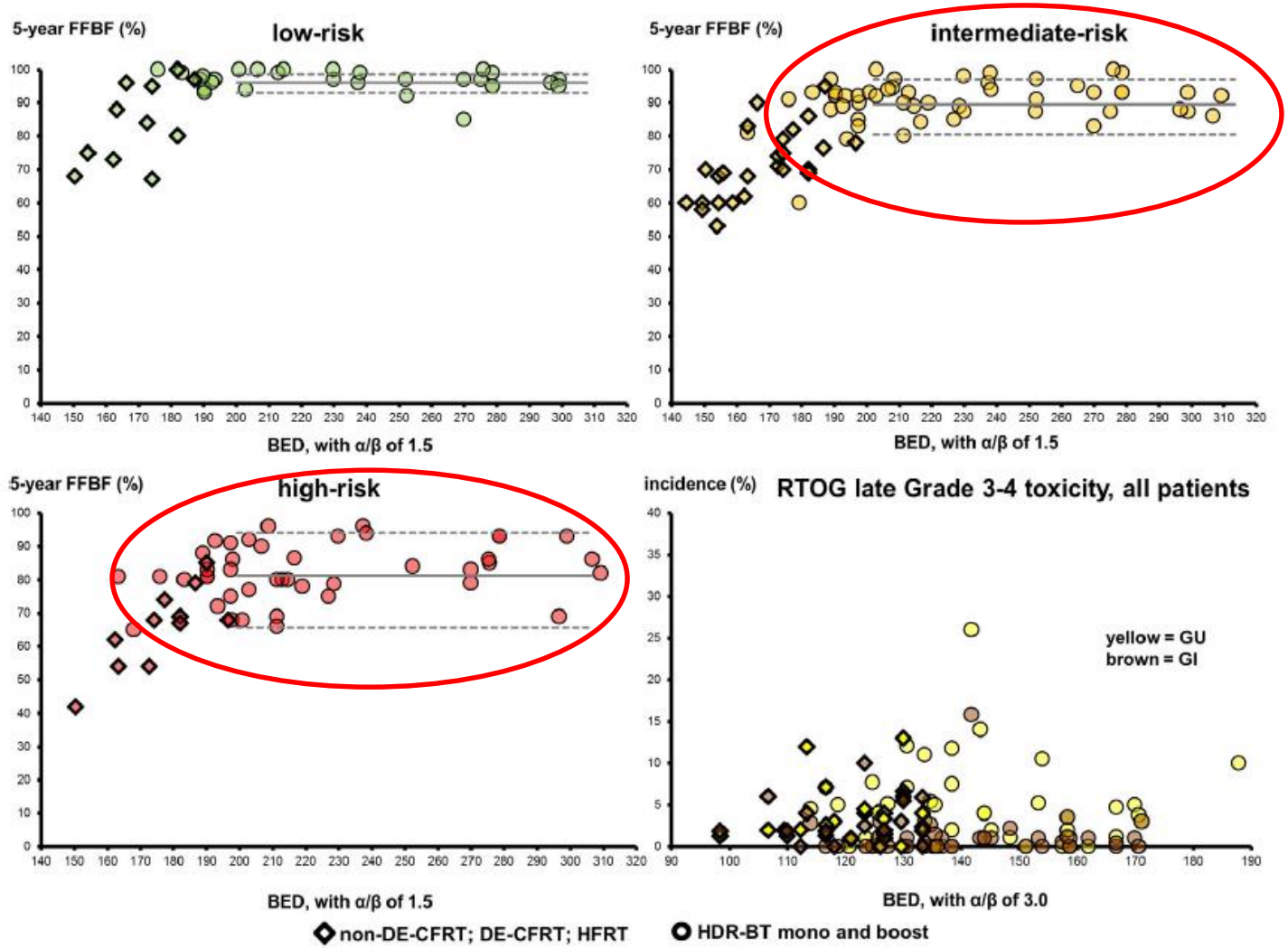
Nicholas G. Zaorsky [a,b,*], Joshua D. Palmer [b], Mark D. Hurwitz [b], Scott W. Keith [c], Adam P. Dicker [b], Robert B. Den [b]

[a] Department of Radiation Oncology, Fox Chase Cancer Center; [b] Department of Radiation Oncology, Sidney Kimmel Cancer Center at Sidney Kimmel Medical College at Thomas Jefferson University; and [c] Department of Pharmacology and Experimental Therapeutics, Division of Biostatistics, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA, USA

5-letnie FFBF ↗200Gy BED

HR: 55%→79%

Brak zysku terapeutycznego BED >200 Gy



Wyniki badań III fazy z eskalacja dawki RT

Phase III Dose Escalation Trials

Author	N	ADT (Hormones)	Freedom from Biochemical Failure	Overall survival	Subgroup BDFS benefit
Kuban (2008)	301	No	73% v 50% (10y, p=0.004)	78% v 79% (8y, p=0.32)	PSA>10
Zietman (2005)	393	No	83% v 68% (10y, p=0.0001)	78% v 83% (10y, p=0.41)	All (low,Int)
Al-Mamgani (2008)	664	Some	54% v 47% (7y, p=0.04)	75% v 75% (7y, p=0.45)	Int, High
Dearnaley (2014)	843	All	55% v 43% (10y, p=0.0003)	71% v 71% (10y, p=0.96)	All
RTOG 0126 (2014)	1499	No	70% v 55% (10y, p<0.0001)	66% v 67% (10y, p=0.87)	Int risk

NRG

Eskalacja dawki RT wpływa znamiennie na podwyższenie 10-letnich przeżyć bez wznowy biochemicznej – 54-**83**%

Wyniki „wysoko-dawkowanej” RT

Table 3 | Improved outcomes with dose-escalated radiotherapy

Study	Design	Conclusions	Comments
Sathya *et al.* (2005)[61]	66 Gy EBRT vs 40 Gy+35 Gy Ir-192 implant	Improved PSA control with additional higher doses with implant	60% high-risk; improved 5-year PSA control 63.3% vs 34.4% in high-risk patients with dose escalation
Peeters *et al.* (2006)[33]	68 vs 78 Gy EBRT	PSA control better in 78 Gy arm	64% high-risk; improved 5-year PSA control 56% vs 48% with dose escalation
Dearnaley *et al.* (2007)[60]	64 vs 74 Gy EBRT (ADT on each arm)	74 Gy improved PSA control	45% high-risk; improved 5-year PSA control 57% vs 43% (HR=0.60) with dose escalation
Zietman *et al.* (2010)[62]	70.2 Gy EBRT vs 79.2 Gy with protons	Better 5-year PSA control with 79.2 Gy	5% high-risk; inadequate sample size of high-risk patients for subset analysis
Kuban *et al.* (2011)[32]	70 vs 78 Gy EBRT	Patients with PSA >10 ng/ml or high-risk benefit from 78 Gy	35% high-risk; 78 Gy improved PSA control (79% vs 57%) and DMFS (96% vs 81%)

Abbreviations: ADT, androgen-deprivation therapy; DMFS, distant metastasis-free survival; EBRT, external beam radiotherapy; Ir-192, Iridium-192; PSA, prostate-specific antigen; vs, versus.

↗ 29%

Podwyższenie dawki o 8-10 Gy zwiększa :

5-letnie przeżycie bez wznowy biochemicznej o 8-29%

i **przeżycie bez odległych przerzutów o 15%**

IGRT – warunek podania należnej dawki RT

International Journal of Radiation Oncology biology • physics
www.redjournal.org

Clinical Investigation: Genitourinary Cancer

Improved Clinical Outcomes With High-Dose Image Guided Radiotherapy Compared With Non-IGRT for the Treatment of Clinically Localized Prostate Cancer

Michael J. Zelefsky, M.D.,* Marisa Kollmeier, M.D.,* Brett Cox, M.D.,* Anthony Fidaleo, B.A.,* Dahlia Sperling, B.A.,* Xin Pei, Ph.D.,* Brett Carver, M.D., Ph.D.,† Jonathan Coleman, M.D.,‡ Michael Lovelock, Ph.D.,† and Margie Hunt, B.S.†

*Departments of Radiation Oncology, †Medical Physics, and ‡Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY

Received Aug 18, 2011, and in revised form Nov 2, 2011. Accepted for publication Nov 14, 2011

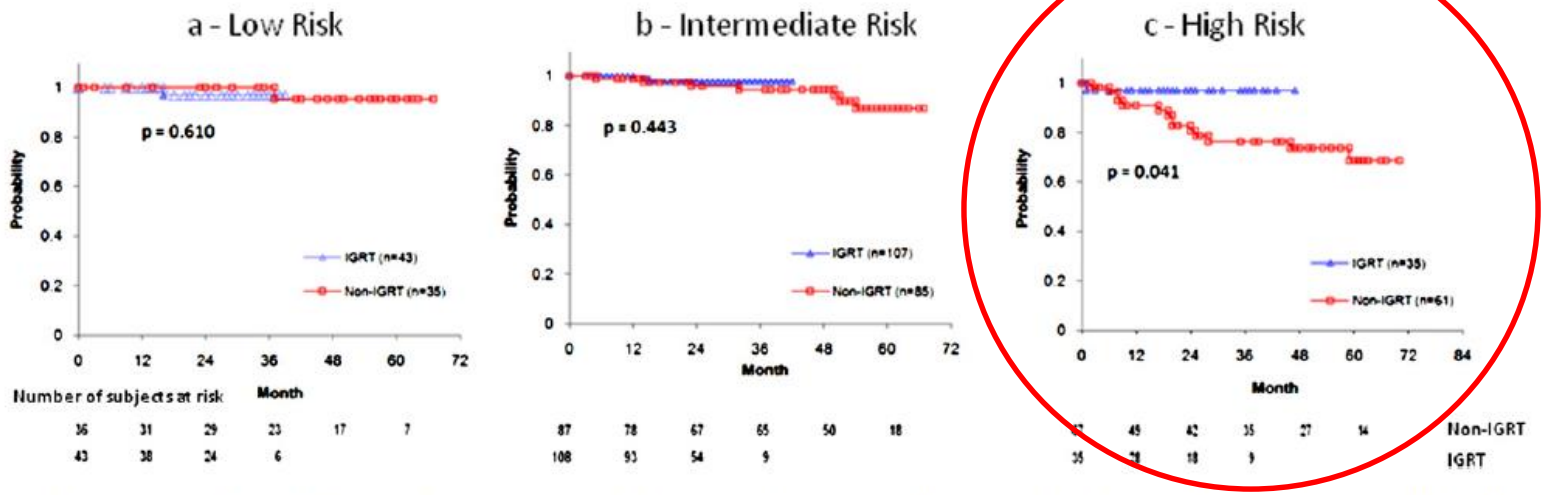


Fig. 2. Comparison of prostate specific antigen relapse-free survival outcomes between patients treated with image-guided radiotherapy (IGRT) to 86.4 Gy and those treated with intensity-modulated radiotherapy to the same dose level.

Zastosowanie techniki IGRT w raku stercza skutkuje zmniejszeniem ryzyka wznowy biochemicznej, zwłaszcza w raku HR

IGRT jest techniką z wyboru w RT raka stercza

International Journal of Radiation Oncology biology • physics
www.redjournal.org

Clinical Investigation: Genitourinary Cancer

Improved Clinical Outcomes With High-Dose Image Guided Radiotherapy Compared With Non-IGRT for the Treatment of Clinically Localized Prostate Cancer

Michael J. Zelefsky, M.D.,* Marisa Kollmeier, M.D.,* Brett Cox, M.D.,* Anthony Fidaleo, B.A.,* Dahlia Sperling, B.A.,* Xin Pei, Ph.D.,* Brett Carver, M.D., Ph.D.,† Jonathan Coleman, M.D.,‡ Michael Lovelock, Ph.D.,† and Margie Hunt, B.S.†

*Departments of Radiation Oncology, †Medical Physics, and ‡Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY

Received Aug 18, 2011, and in revised form Nov 2, 2011. Accepted for publication Nov 14, 2011

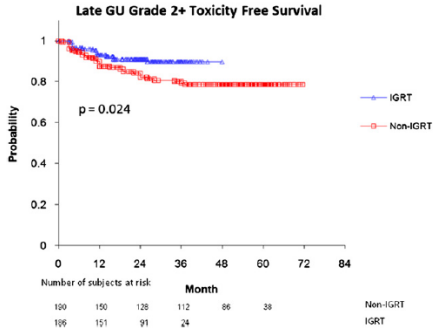


Fig. 1. Comparison of actuarial likelihood of grade 2 or higher late urinary toxicity for patients treated with image-guided radiotherapy (IGRT) to 86.4 Gy vs. intensity-modulated radiotherapy.

Table 2 Comparison of acute rectal and urinary toxicities between patients treated with IGRT and non-IGRT

	IGRT (n = 186)		Non-IGRT (n = 190)		Total (n = 376)	
Acute toxicities	n	%	n	%	n	%
Rectal						
0	141	75.8	155	81.6	296	78.7
1	43	23.1	32	16.8	75	19.9
2	2	1.1	2	1.1	4	1.1
3	0	0.0	1	0.5	1	0.3
Urinary						
0	37	19.8	73	38.5	110	29.3
1	115	61.8	66	34.7	181	48.1
2	34	18.4	51	26.8	85	22.6
3	0	0.0	0	0.0	0	0.0
Total	186		190		376	

Abbreviation: IGRT = image-guided radiotherapy.

Table 3 Cox regression analysis for predictors of late urinary toxicity

Cox regression	Coefficient	95% CI (±)	SE	p	Hazard exponent coefficient
Age	0.028	0.041	0.021	0.183	1.028
Androgen deprivation therapy	0.150	0.566	0.288	0.603	1.161
IGRT	0.711	0.606	0.309	0.021	2.037
Baseline IPSS	0.043	0.036	0.018	0.021	1.044

Abbreviations: CI = confidence interval; IGRT = image-guided radiotherapy; IPSS = International Prostate Symptom Score; SE = standard error.

IGRT → zmniejszenie ryzyka wczesnej toksyczności stopnia 2 i zmniejszenie ryzyka *późnej toksyczności stopnia ≥2* ze strony układu moczowego

376 chorych

Toksyczność wczesna stopnia ≥3 po IGRT – 0%, po nie-IGRT – ukł. pok. – 0,5%

Ruchomość gruczołu krokowego

Therapist vs Physician Registration

Differences ≥ 5 mm

Marker	Anatomy	Contour
A/P: 1 % S/I: 2 % Lat: 1 %	A/P: 5 % S/I: 10 % Lat: 0 %	A/P: 17 % S/I: 31 % Lat: 3 %

Int J Radiat Oncol Biol Phys. 2006 Aug 1;65(5):1561-72.

Initial experience with megavoltage (MV) CT guidance for daily prostate alignments.

Langen KM[1], Zhang Y, Andrews RD, Hurley MC, Meeks SL, Poole DJ, Willoughby TR, Kupelian PA

Margines CTV-PTV

Institution	CTV-PTV Margin (mm)
UM	5 everywhere
Beaumont	Adaptive based on wk 1 helical CBCT (5 scans)
Wash U	5 everywhere
Peter Mac	7 post, 10 elsewhere
Duke	5 everywhere
Cedars	5 everywhere
ROC	4 posteriorly, 6 inf, 5 elsewhere
MCW	3 post, 5 elsewhere
Mayo	4-5 post, 5-7 laterally, 5 elsewhere
MSKCC	6 everywhere
FCCC	3-5 mm post, 6-8 elsewhere

Pooperacyjna RT (CTV-PTV)

- 10mm
- 6mm post

ASTRO 58th 2016 Contouring Guidelines and Tips for Prostate Cancer Radiotherapy Michael M. J Zelefsky M.D.E Finkelstein, M.D

Dawki krytyczne

- <30% ściany odbytnicy 75.6Gy
- <53% ściany odbytnicy do 47Gy
- Dmax ściana odbytnicy 83.4Gy (dawka całkowita 81Gy)
- Dmax Jelito grube <60Gy

ASTRO 58th 2016 Contouring Guidelines and Tips for Prostate Cancer Radiotherapy Michael M. J Zelefsky M.D.E Finkelstein, M.D

- <=50% odbytnicy 50Gy
- <=20% odbytnicy 70Gy

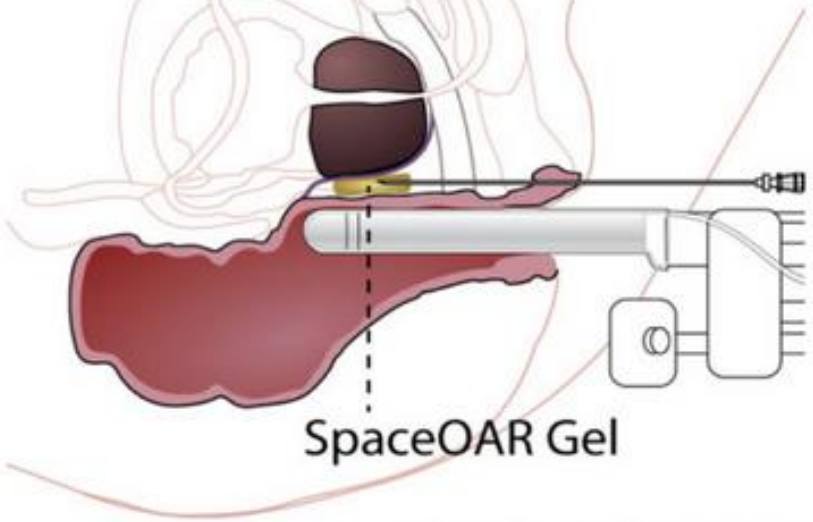
RTOG GU Radiation oncology specialists reach consensus on pelvic lymph node volumes for high-risk prostate cancer.

Redukcja toksyczności ze strony odbytnicy

Spacery

- Aplikacja pomiędzy powięzią Denonvilliers, a ścianą odbytnicy
- Wykonywana pod kontrolą TRUS
- Aplikacja przezkroczowa

Insertion technique of SpaceOAR Gel. Courtesy of Augmenix, MA, USA.



BJU Int. 2014 Mar;113 Suppl 2:13-20. doi: 10.1111/bju.12624.

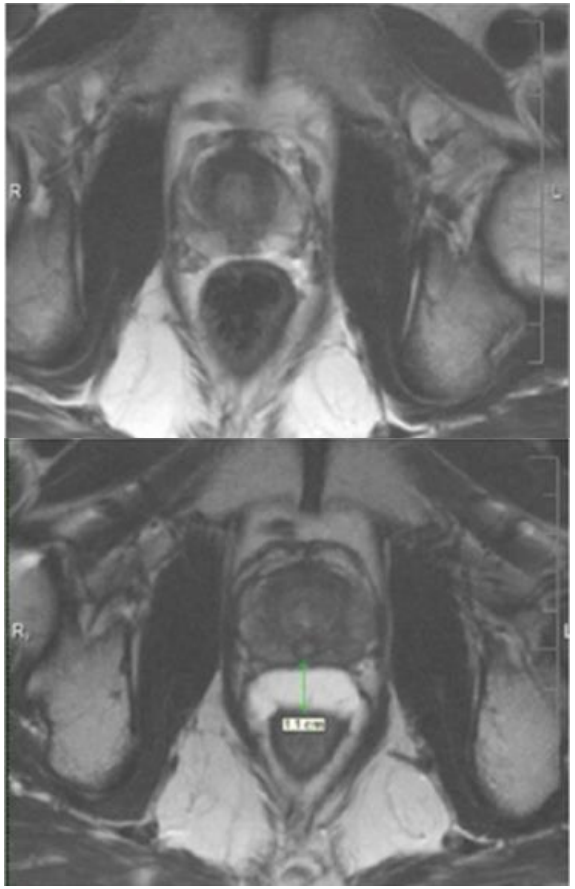
Fiducial markers and spacers in prostate radiotherapy: current applications.

Ng M[1], Brown E, Williams A, Chao M, Lawrentschuk N, Chee R.

Redukcja toksyczności ze strony odbytnicy

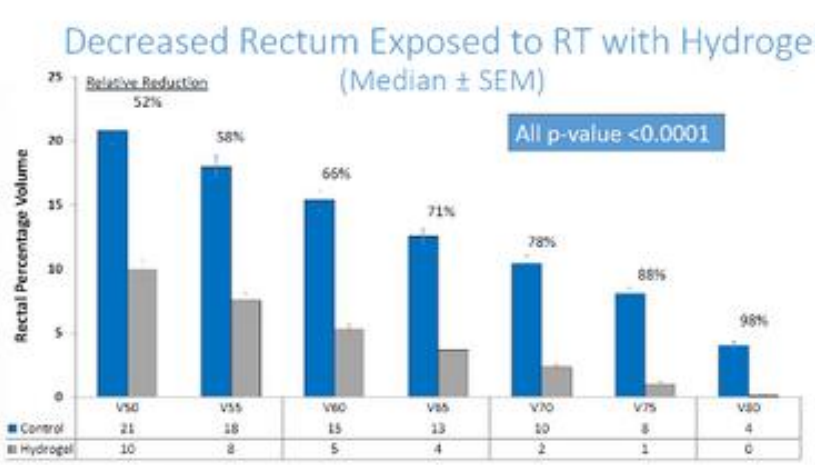
- Kwas hialuronowy
- Krew
- Kolagen
- Hydrogel
- Biodegradowalny balon
- Polyethyleno-glycol (PEG)

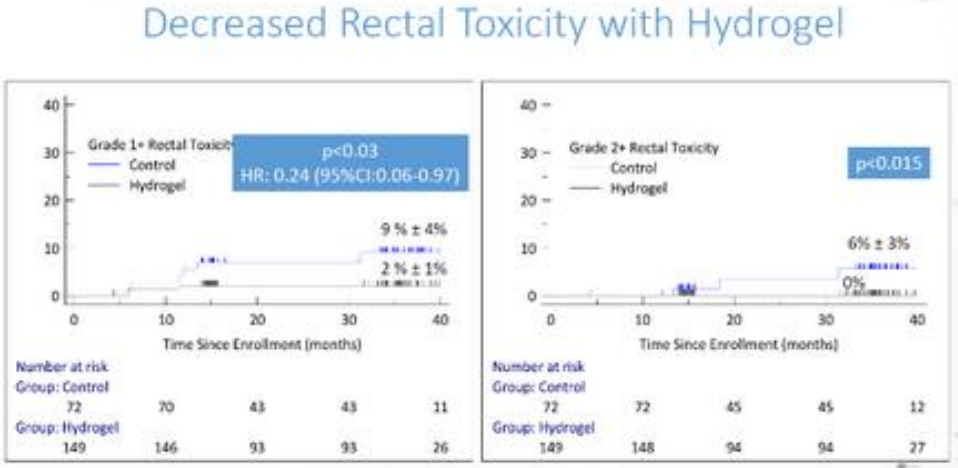
Spacery-Rodzaje



Redukcja procentowej objętości odbytnicy otrzymującej dawkę średnią (V50 – 52%, V80 – 98%, p=0,0001),
zmniejszenie toksyczności ≥2 stopnia ze strony odbytnicy (p=0,015)

Spacery-Badania III fazy-222pts



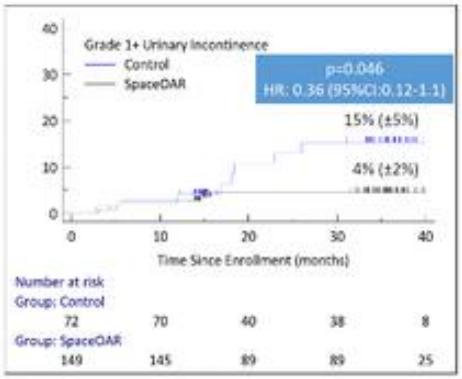


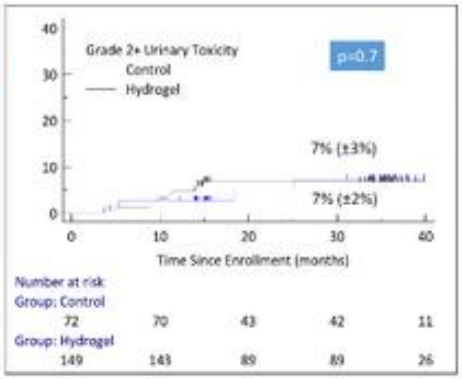
ASTRO 2016 Daniel A. Hamstra, MD, PhD Texas Oncology
Continued Benefit to Rectal Separation for Prostate RT: Final Results of a phase III trial

Redukcja ryzyka powikłań ze strony układu moczowego stopnia 3, głównie nietrzymania moczu (*15%→4%, p=0,066*), poprawa jakości życia w ocenie funkcjonowania przewodu pokarmowego (p=0,002)

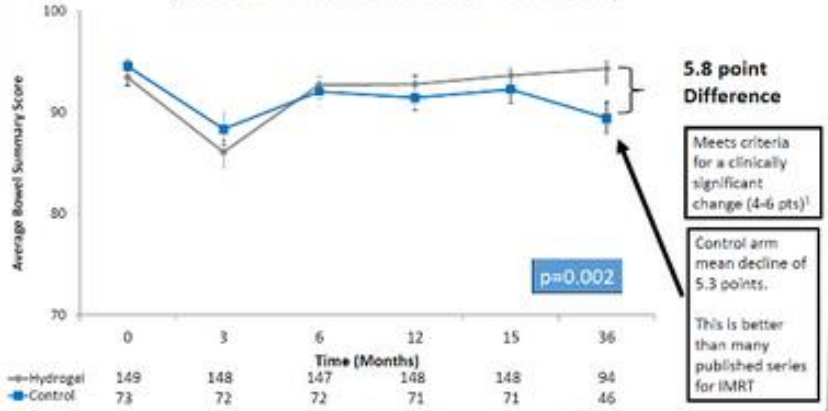
Spacery-Badania III fazy-222pts

Decreased Urinary Incontinence with Hydrogel





Bowel Quality of Life Better with Hydrogel
(Mean ± Standard Error of Mean)



ASTRO 2016 Daniel A. Hamstra, MD, PhD Texas Oncology
Continued Benefit to Rectal Separation for Prostate RT: Final Results of a phase III trial

Quality of life after radiotherapy for prostate cancer with a hydrogel spacer – five year results

Michael Pinkawa[1,2], Vanessa Berneking[1,2], Marsha Schlenter[1], Barbara Krenkel[1], Michael J. Eble[1]

1. Department of Radiation Oncology, University Hospital RWTH Aachen, Germany
2. Department of Radiation Oncology, MediClin Robert Janker Klinik Bonn, Germany

healing art and science of radiation oncology

In the years 2010-2011, 114 patients received an external beam radiotherapy to the prostate without pelvic lymph nodes in our department. Depending on the patient's and responsible radiation oncologist's preference, 54 patients were selected for a hydrogel injection before the beginning of RT.

Istotne zmniejszenie toksyczności ≥2 stopnia ze strony odbytnicy po zastosowaniu spacerów!!!

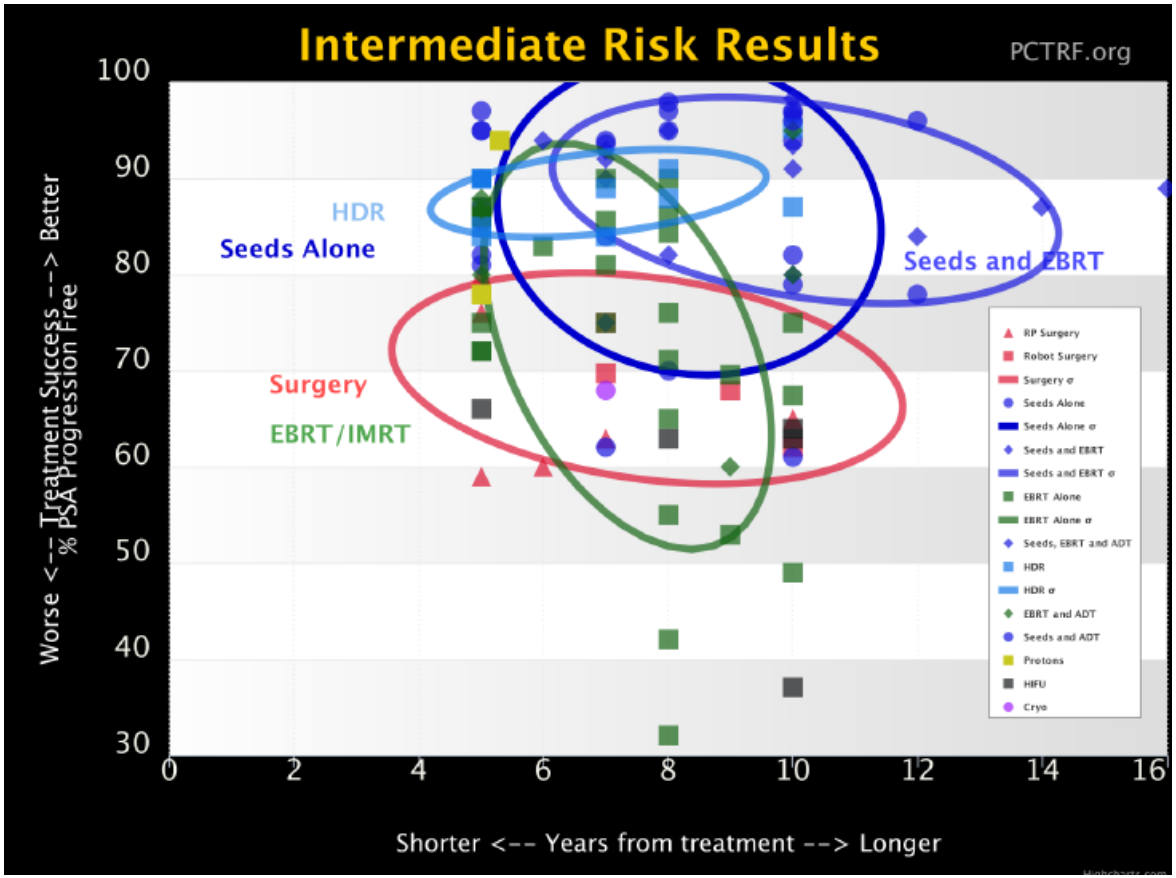
Table 2. Quality of life one and five years after radiotherapy (positive number corresponds to decreasing score).

		with spacer (n=54)	without spacer (n=60)	p-value
mean (quartiles) urinary bother score change	1.5 years after RT	-2 (-7;0;4)	-3 (-11;-4;4)	0.49
mean (quartiles) bowel bother score change		-1 (0;0;0)	7 (-4;0;14)	0.13
mean (quartiles) sexual bother score change		13 (0;6;31)	18 (0;19;42)	0.28
moderate/big problem with bowel urgency		0	13	<0.01
moderate/big problem with losing control of stools		0	9	0.03
moderate/big problem with bowel habits overall		0	17	<0.01
mean (quartiles) urinary bother score change	5 years after RT	0 (-5;0;7)	-3 (-9;-4;4)	0.22
mean (quartiles) bowel bother score change		1 (0;0;4)	6 (-4;0;11)	0.99
mean (quartiles) sexual bother score change		21 (0;9;39)	28 (-6;31;75)	0.77
moderate/big problem with bowel urgency		0	14	0.01
moderate/big problem with losing control of stools		0	7	0.09
moderate/big problem with bowel habits overall		0	7	0.08

SUMMARY / CONCLUSION

The first five-year quality of life results in a group of prostate cancer patients treated with a hydrogel spacer demonstrate excellent treatment tolerability, in particular regarding bowel problems. Further studies with dose-escalated or re-irradiation concepts can be encouraged.

Porównanie skuteczności leczenia (przeżycie bez wznowy biochemicznej) w grupie IR



2017

Najskuteczniejsze:

BT LDR, BT HDR / EBRT + BT LDR

Analiza obejmuje ponad 44 tysięcy artykułów na temat raka gruczołu krokowego opublikowanych w latach 2000 – 2015, z których 1415 było poświęcone wynikom leczenia.

Brachyterapia HDR – monoterapia w IR PCa

doskonała tolerancja leczenia , wysokie odsetki bRFS

Study (reference)	n	M. follow-up (yrs)	Risk	HDR schedule	ADT	Toxicity score	G2 GI late toxicity	G3 GI late toxicity	G2 GU late toxicity	G3 GU late toxicity	bRFS*
Demanes (1)	298	5.2	L 81%, I 18%, H 1%	6 × 7 Gy (53%) 4 × 9.5 Gy (47%)	24%	CTCAE 3.0	<1%	<1%	10%	3%	97%
Zamboglou (2)	718	4.4	L 55%, I 25%, H 20%	4 × 9.5 Gy (68%) 3 × 11.5 Gy (32%)	21.4%	CTCAE 3.0	~1%	1.6%	~20%	3.5%	94%
Yoshioka (3)	112	5.4	L 13%, I 26%, H 61%	9 × 6 Gy	84%	CTCAE 3.0	12%#	3%#	12%#	3%#	83%
Hoskin (4)	197	0.5-5	L 4%, I 52%, H 44%	4 × 8.5 Gy (15%) 4 × 9 Gy (13%) 3 × 10.5 Gy (55%) 2 × 13 Gy (17%)	80%	RTOG	1%	4-13%	20-30%	3-14%	95%
Rogers (5)	284	2.7	I 100%	6 × 6.5 Gy	16%	RTOG	0%	0%	1.8%	0.7%	83%
Present study	36	6.9	L 78%, I 22%	4 × 9,5 Gy	14%	CTCAE 3.0	0%	0%	28%	19%	97%

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 14, 2011 VOL. 365 NO. 2

Radiotherapy and Short-Term Androgen Deprivation for Localized Prostate Cancer

Christopher U. Jones, M.D., Daniel Hunt, Ph.D., David G. McGowan, M.B., Ch.B., Mahul B. Amin, M.D., Michael P. Chetner, M.D., Deborah W. Bruner, R.N., Ph.D., Mark H. Leibenhaut, M.D., Siraj M. Husain, M.D., Marvin Rotman, M.D., Luis Souhami, M.D., Howard M. Sandler, M.D., and William U. Shipley, M.D.

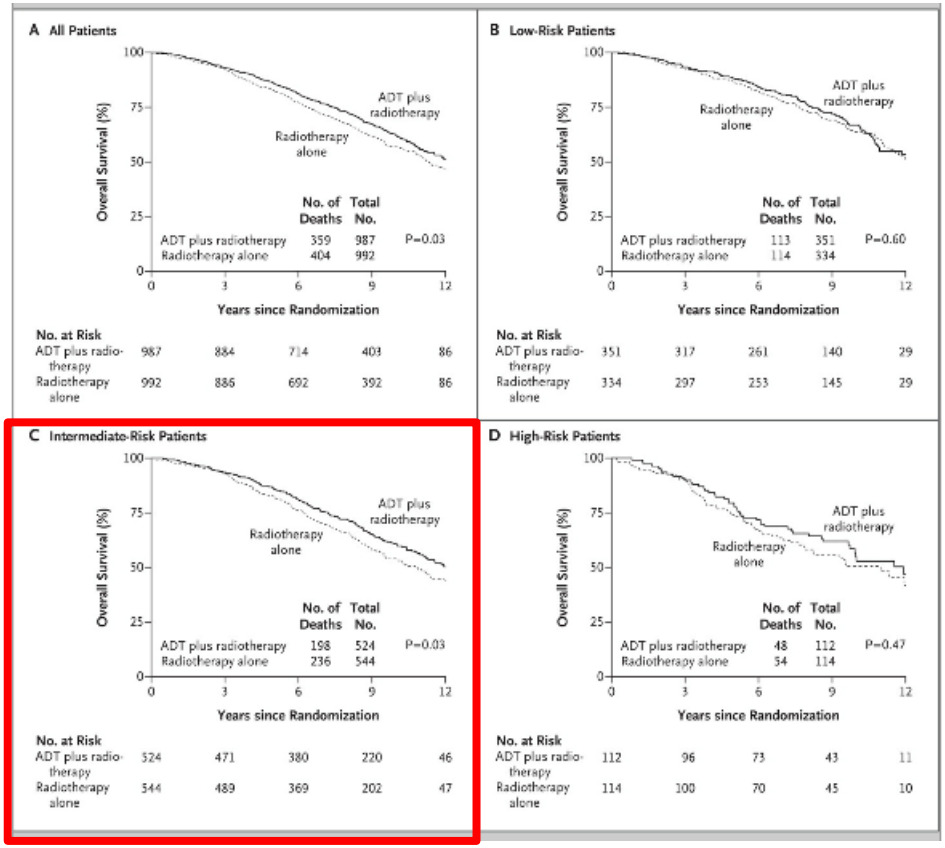
IR rekomendacja dla 4-6 mies. ADT

Wnioski

Chorzy T1b, T1c, T2a lub T2b i PSA ≤20 ng/ml odnoszą korzyść z krótkotrwałej ADT stosowanej przez 4 mies. (2 przed, 2 w trakcie RT

Obserwuje się istotne statystycznie zmniejszenie śmiertelności specyficznej dla raka i wydłużenie ogólnego przeżycia.

W analizie *post hoc risk* zysk dotyczy przede wszystkim chorych z grupy pośredniego ryzyka, bez wpływu w grupie niskiego ryzyka progresji.



Podstawa rekomendacji NCCN dla grupy pośredniego ryzyka progresji

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 14, 2011 VOL. 365 NO. 2

Radiotherapy and Short-Term Androgen Deprivation for Localized Prostate Cancer

Christopher U. Jones, M.D., Daniel Hunt, Ph.D., David G. McGowan, M.B., Ch.B., Mahul B. Amin, M.D., Michael P. Chetner, M.D., Deborah W. Bruner, R.N., Ph.D., Mark H. Leibenhaut, M.D., Siraj M. Husain, M.D., Marvin Rotman, M.D., Luis Souhami, M.D., Howard M. Sandler, M.D., and William U. Shipley, M.D.

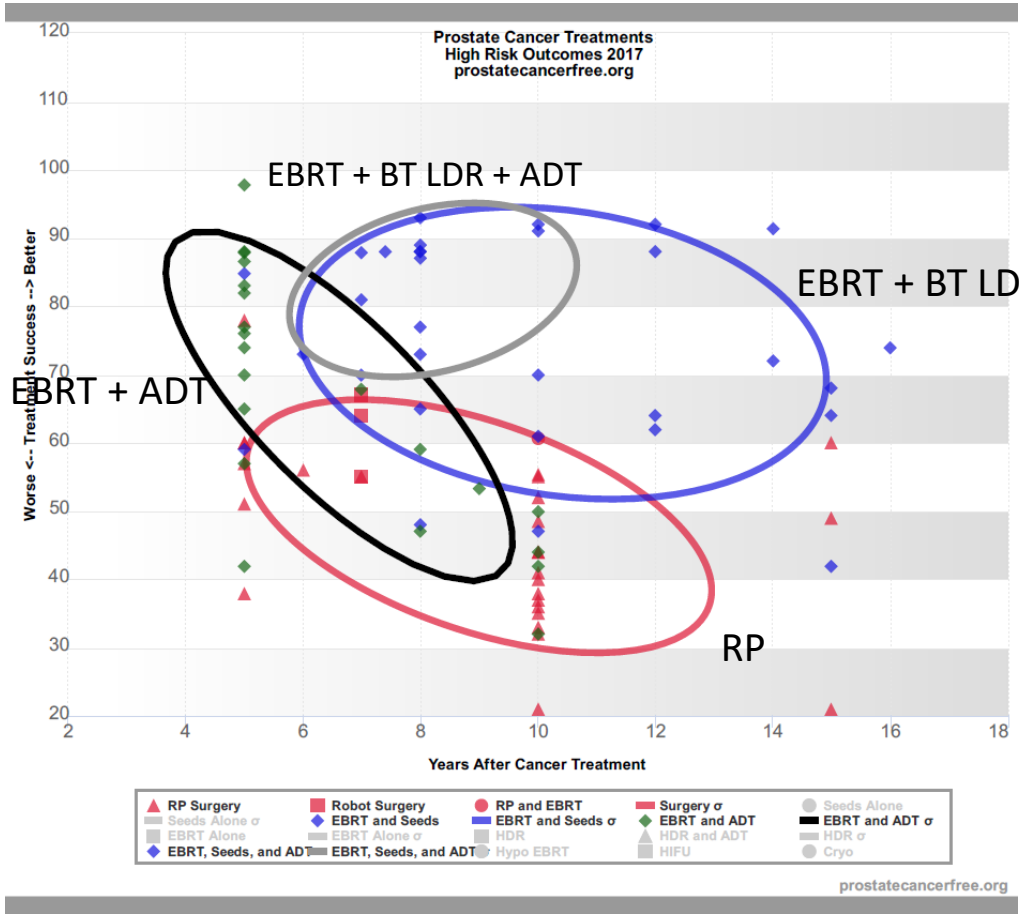
Table 1. Pretreatment Characteristics

Characteristic	Treatment: ADT and EBRT (n = 224) No.	%	EBRT Alone (n = 232) No.	%
Age, years				
Median	70		71	
Range	50-88		49-84	
PSA				
No.	64		67	
Median	22.6		33.8	
Range	2.2-128		1.9-264.6	
Karnofsky PS				
60	1	< 1	0	0
70	2	1	0	0
80	15	7	10	4
90	119	53	125	54
100	87	39	97	42
Institutional Gleason				
3-6	77	45	90	47
7-10	96	55	103	53
Missing	51		39	
Central Gleason				
3-6	70	33	59	27
7-10	145	67	156	73
Missing	9		17	
Group stage				
B2	64	29	71	31
C	160	71	161	69

- **Wyniki**
- 10-letnie OS w grupie RT+ADT vs RT (43% *v* 34%) i średni czas przeżycia (8.7 *v* 7.3 lat) wskazują na kliniczny zysk z dodania 4-miesięcznej ADT jakkolwiek bez istotności statystycznej (*P* .12).
- Statystycznie istotna poprawa z dodania ADT do RT w zakresie 10-lat DSM (23% *v* 36%; *P* .01), DM (35% *v* 47%; *P* .006), DFS (11% *v* 3%; *P* .0001) i BF (65% *v* 80%; *P* .0001)
- Dodanie ADT bez wpływu na ryzyko powikłań sercowo-naczyniowych.

Podstawa rekomendacji NCCN dla grupy pośredniego ryzyka progresji

Porównanie skuteczności leczenia (przeżycie bez wznowy biochemicznej) w grupie HR



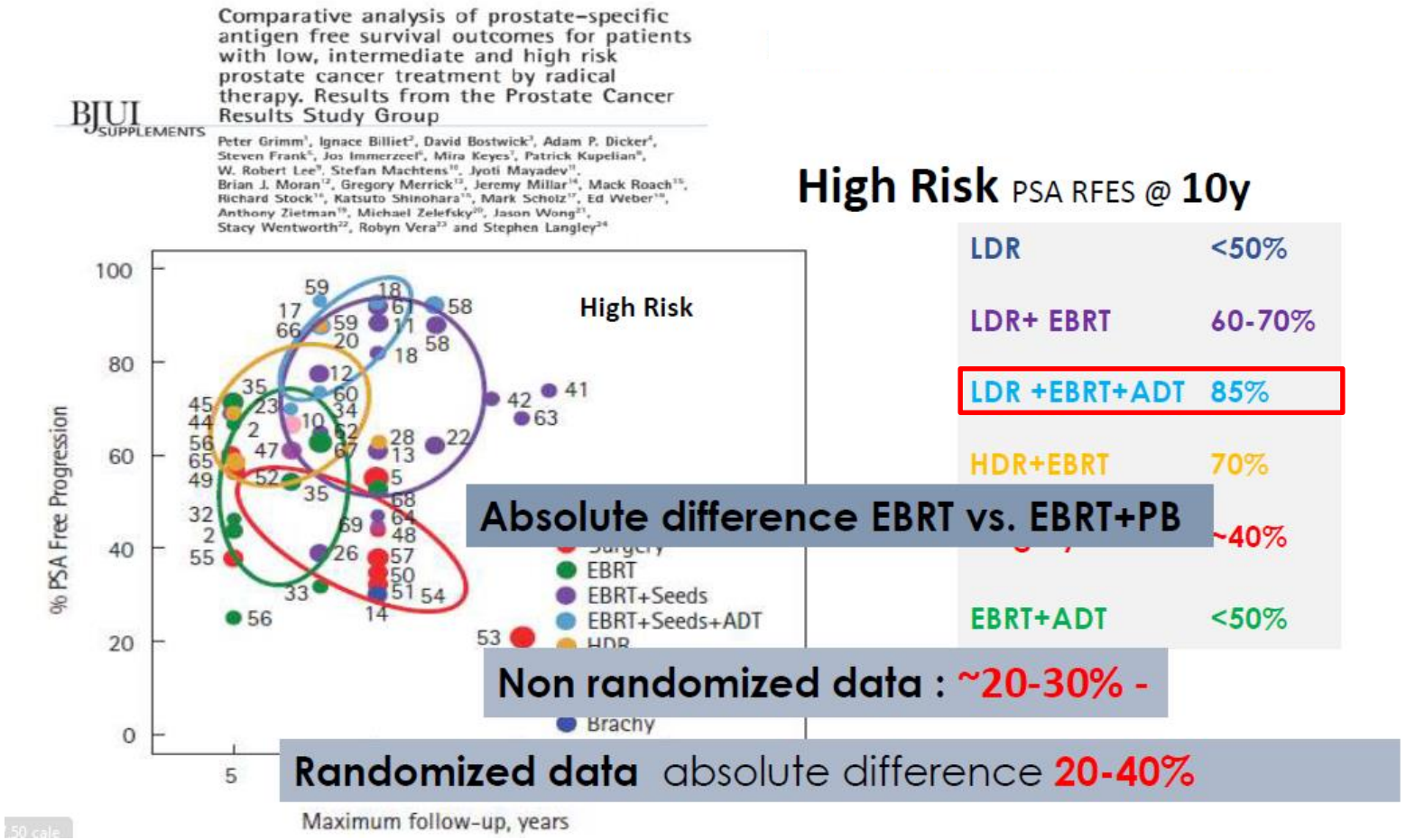
2017

Najskuteczniejsze:

EBRT + BT LDR + ADT / EBRT + BT LDR

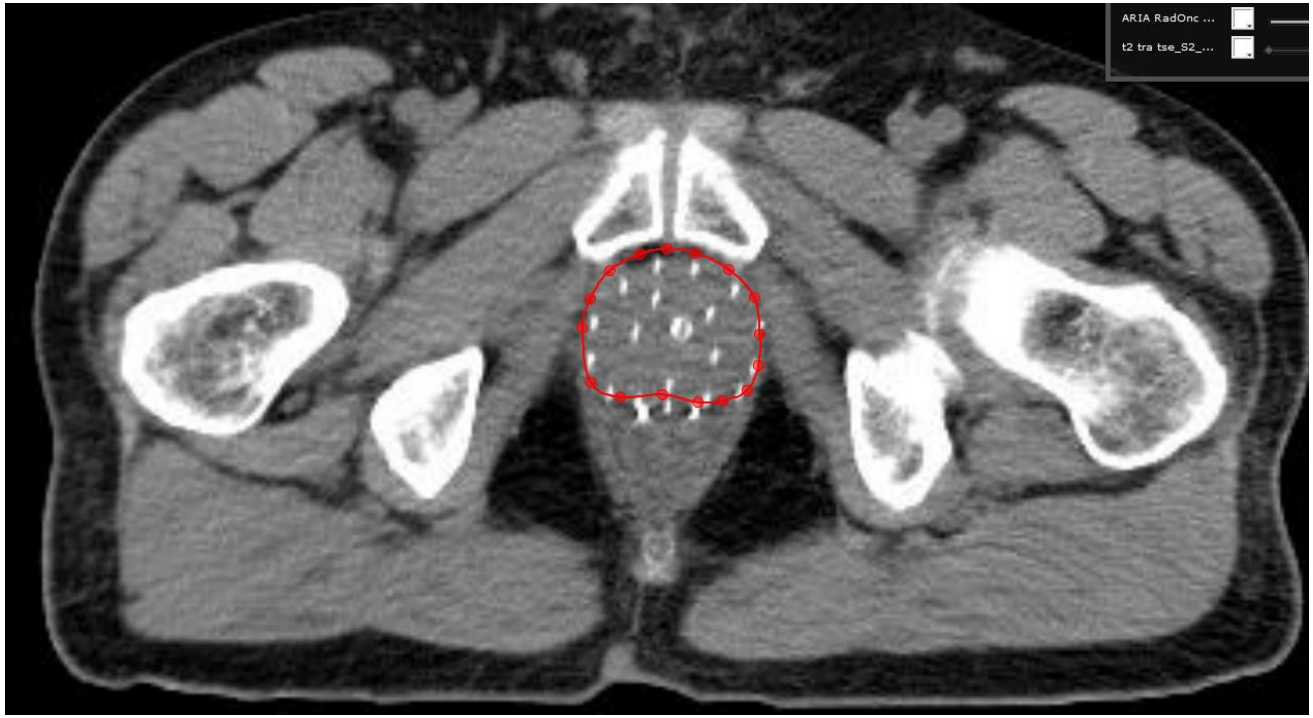
Analiza obejmuje ponad 44 tysięcy artykułów na temat raka gruczołu krokowego opublikowanych w latach 2000 – 2015, z których 1415 było poświęcone wynikom leczenia.

Eskalacja dawki EBRT + BT + ADT

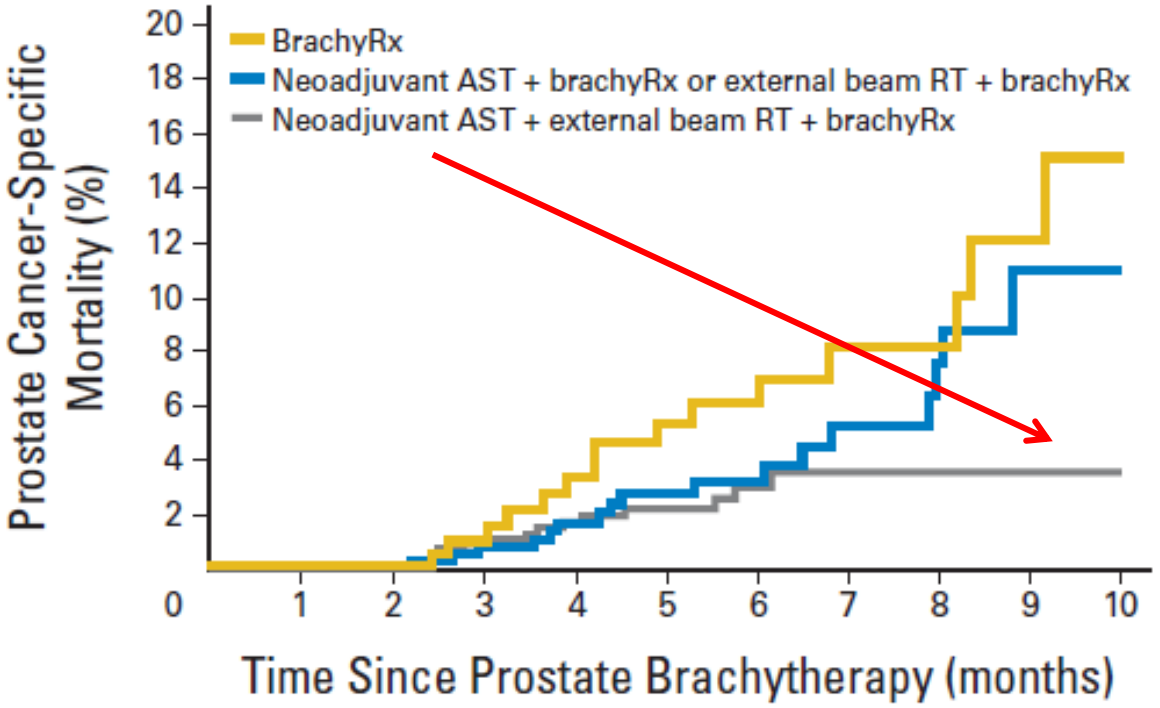


Optymalne skojarzenie EBRT + BT + ADT; 10-letnie przeżycie – **85**%, zysk z dołączenia BT do EBRT **20-40**%

Zastosowanie EBRT+BT+ADT w grupie HR



Skojarzenie EBRT+ADT+BT (źródła stałe) u chorych z grupy wysokiego i bardzo wysokiego ryzyka progresji

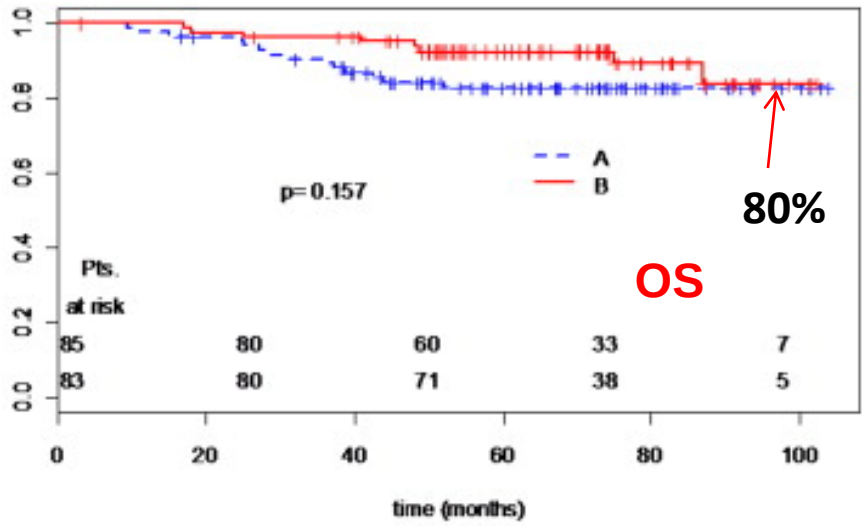


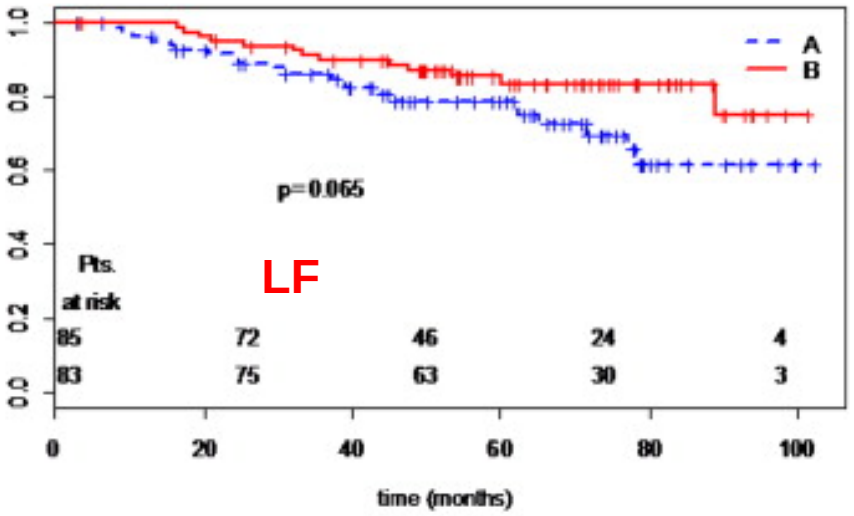
Skojarzenie ADT z BT+EBRT zmniejsza ryzyko śmiertelności specyficznej dla raka stercza <4%

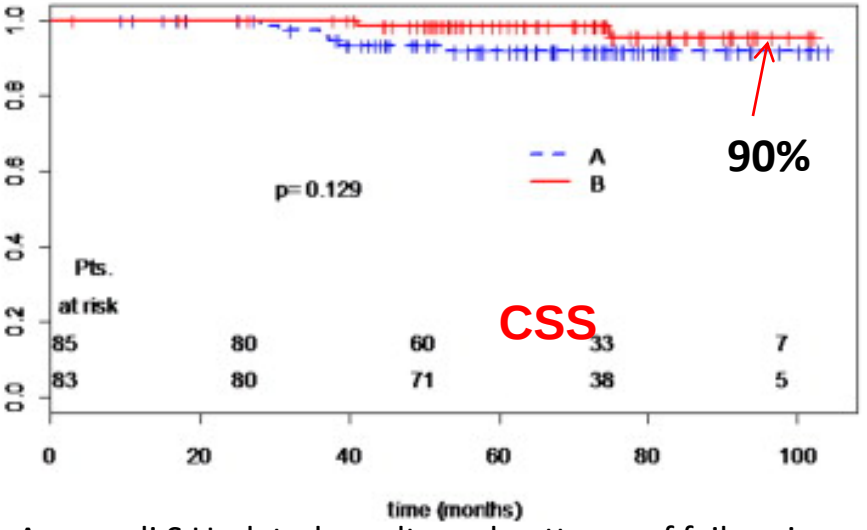
D'Amico AV, Moran BJ, Braccioforte MH et al. Risk of death from prostate cancer after brachytherapy alone or with radiation, androgen suppression therapy, or both in men with high-risk disease. J Clin Oncol. 2009:3923-8

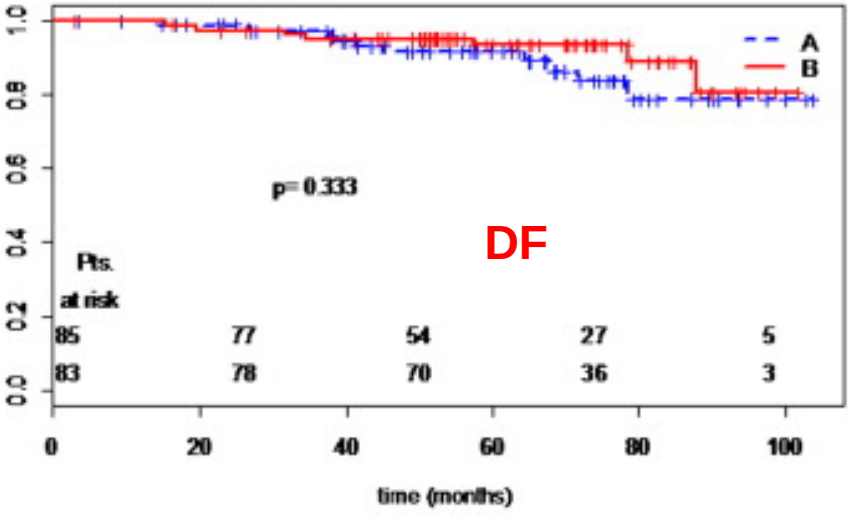
Hipofrakcjonowanie w RT raka stercza

Hipofrakcjonowanie w RT raka stercza









Arcangeli S Updated results and patterns of failure in a randomized hypofractionation trial for high-risk prostate cancerInt J Radiat Oncol Biol Phys. 2012 Dec 1;84(5):1172-8

Hipofrakcjonowanie w RT raka stercza

Hypofractionated radiotherapy versus conventionally fractionated radiotherapy for patients with intermediate-risk localised prostate cancer: 2-year patient-reported outcomes of the randomised, non-inferiority, phase 3 CHHiP trial

Anna Wilkins, Helen Mossop, Isabel Syndikus, Vincent Khoo, David Bloomfield, Chris Parker, John Logue, Christopher Scrase, Helen Patterson†, Alison Birtle, John Staffurth, Zafar Malik, Miguel Panades, Chinnamani Eswar, John Graham, Martin Russell, Peter Kirkbride, Joe M O'Sullivan, Annie Gao, Clare Cruickshank, Clare Griffin, David Dearnaley, Emma Hall**

Lancet Oncol 2015; 16: 1605–16

74 Gy in 37 fractions (n=676)	60 Gy in 20 fractions (n=686)	57 Gy in 19 fractions (n=692)

Wnioski:

Toksyczność umiarkowanie hipofrakcjonowanej RT (3-3,1 Gy/fr) nie różni się od RT frakcjonowanej konwencjonalnie (2 Gy/fr.) w zakresie:

- przewodu pokarmowego
- układu moczowego
- funkcji seksualnych

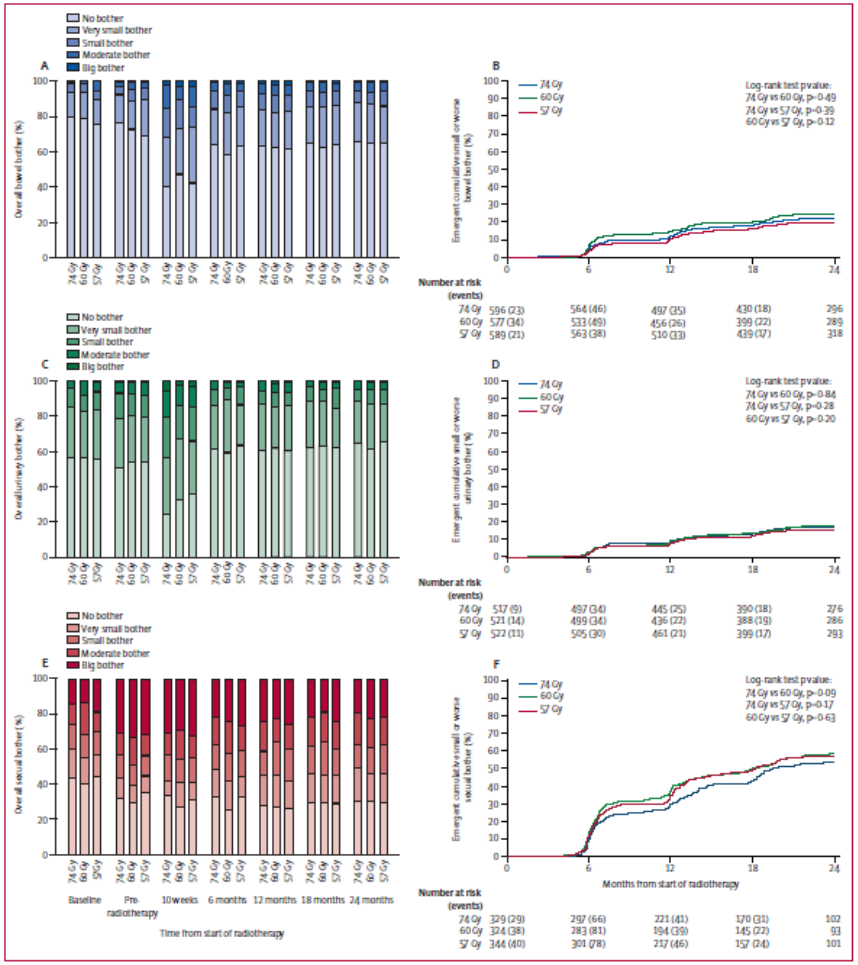


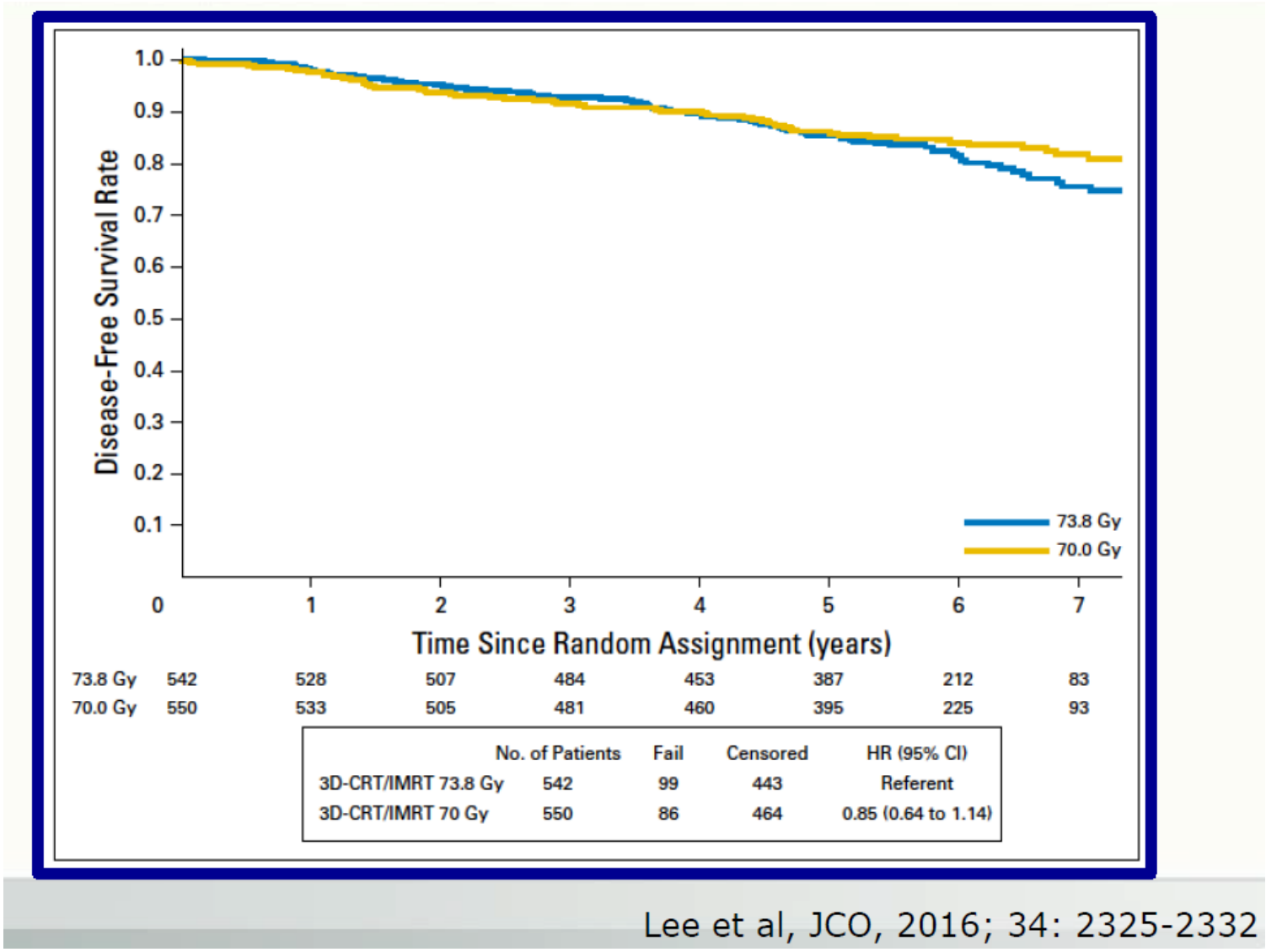
Figure 2: Overall bowel, urinary, and sexual bother
Data are prevalence of overall bowel bother (A), time to small or worse overall bowel bother (B), prevalence of overall urinary bother (C), time to small or worse overall urinary bother (D), prevalence of overall sexual bother (E), and time to small or worse overall sexual bother (F).

Hipofrakcjonowanie w RT raka stercza

Phase 3 trials of moderate hypofractionation in prostate cancer			
Sponsor	**Sample size**	**Risk group**	**Regimens tested**
RTOG 0415	1067	Low	73.8/1.8 Gy v 70/2.5 Gy
OCOG (Canada)	1204	Intermediate	78/2 Gy v 60/3 Gy
CHHIP (UK)	3216	Low/Intermediate/High	74/2 Gy v 57/3 Gy v 60/3 Gy
HYPRO (Dutch)	820	Int/High	78/2 Gy v 64.6/3.4 Gy (3 fractions/week)

Hipofrakcjonowanie w RT raka stercza

DFS



Lee et al, JCO, 2016; 34: 2325-2332

Hipofrakcjonowanie w RT raka stercza

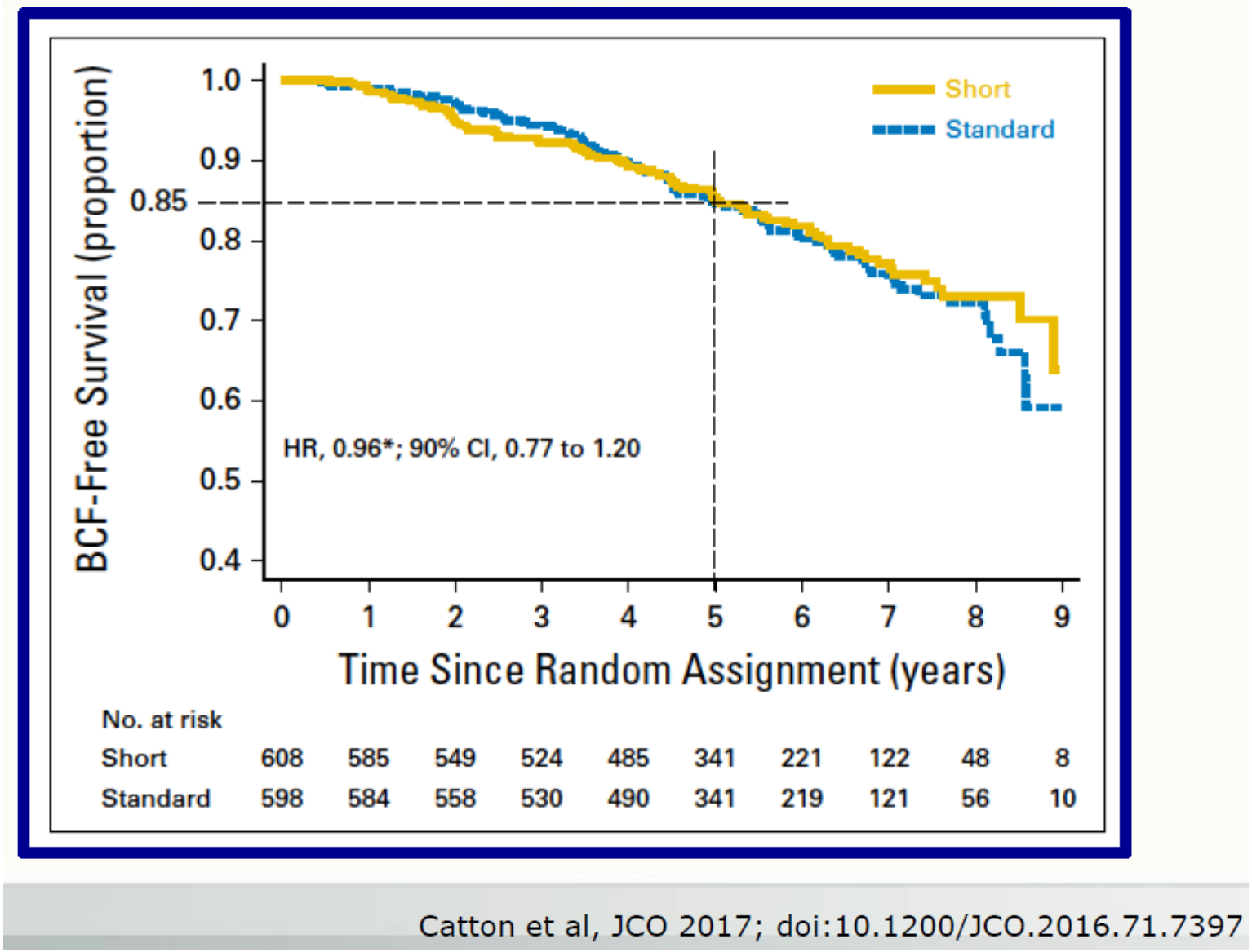
Adverse event	Standard	Hypo	RR (95% CI)	P-value
Late Gastrointestinal toxicity				
Grade 2	11.4	18.3	1.59 (1.22-2.06)	0.005
Grade ≥3	2.6	4.1	1.55 (0.8-2.99)	0.19
Late Urinary toxicity				
Grade 2	20.5	26.2	1.31 (1.07-1.61)	0.009
Grade ≥3	2.3	3.5	1.56 (0.76-3.18)	0.22

Wyższe ryzyko późnej toksyczności GI i GU 2 stopnia, nieistotnie wyższe 3 stopnia!!!

Lee et al, JCO, 2016; 34: 2325-2332

Hipofrakcjonowanie w RT raka stercza

bFFS



Catton et al, JCO 2017; doi:10.1200/JCO.2016.71.7397

Hipofrakcjonowanie w RT raka stercza

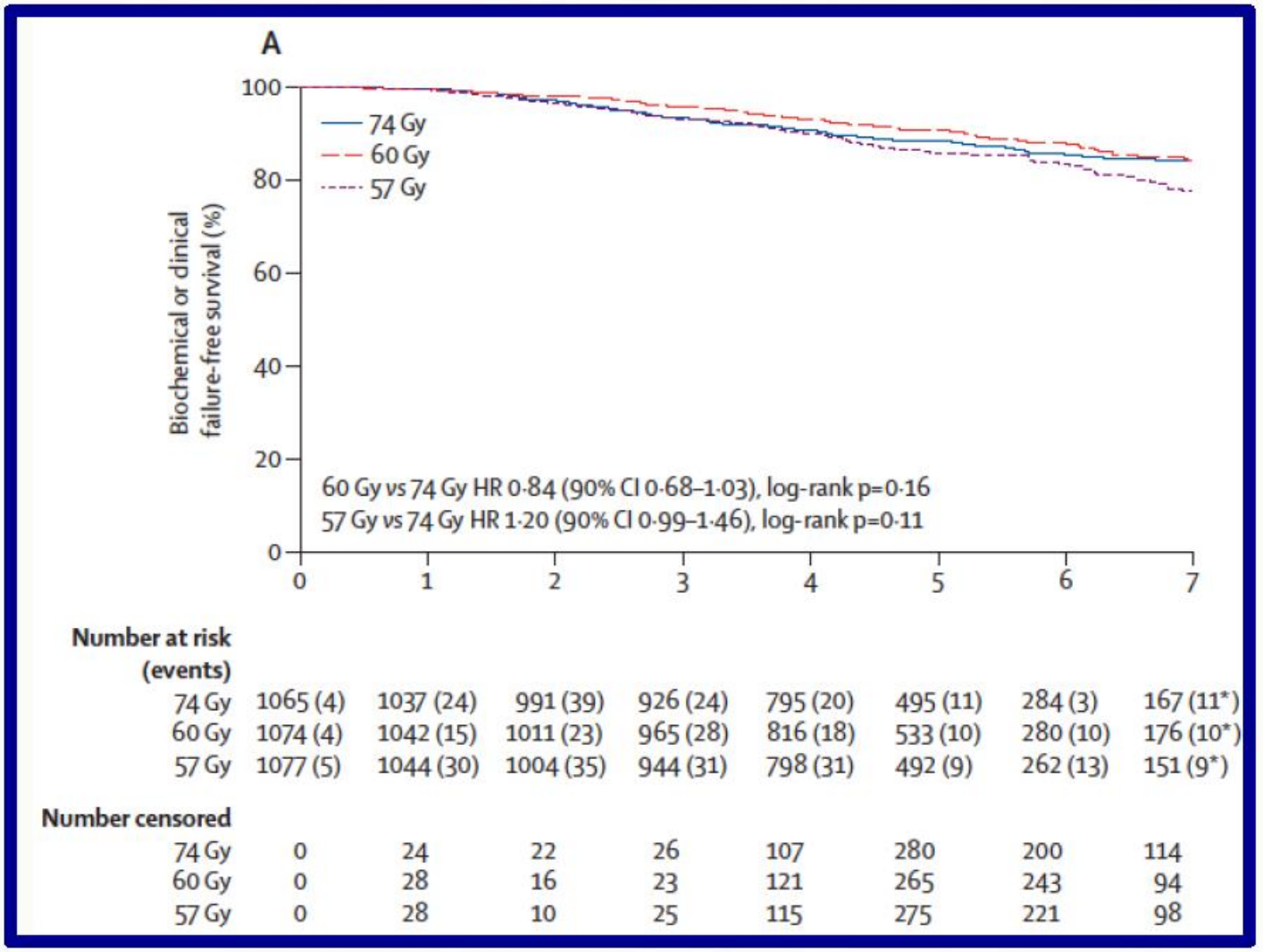
Gastro-intestinal toxicity				
	Acute toxicity (%)		*Late toxicity (%)*	
Grade	*Short*	*Standard*	*Short*	*Standard*
0	41	48	58	52
1	43	42	33	34
2	16	10	7.4	11
3	0.7	0.5	1.5	2.7
4	0	0	0	0.2

Wyższe ryzyko wczesnej toksyczności GI 2 stopnia, nieistotnie wyższe 3 stopnia, niższe ryzyko późnej toksyczności GI 2 i 3 stopnia!!!

Catton et al, JCO 2017; doi:10.1200/JCO.2016.71.7397

Hipofrakcjonowanie w RT raka stercza

bFFS

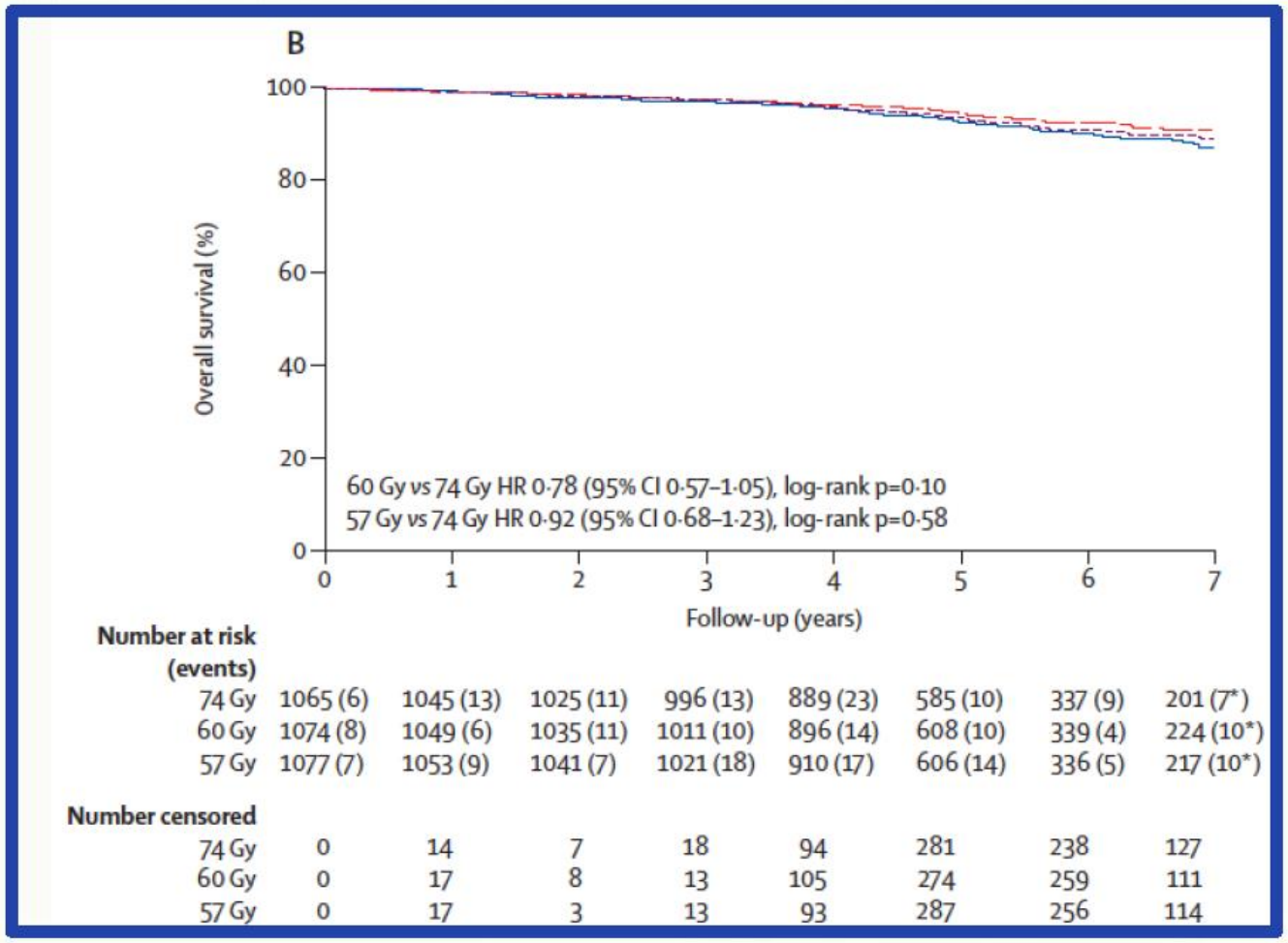


Number at risk (events)								
74 Gy	1065 (4)	1037 (24)	991 (39)	926 (24)	795 (20)	495 (11)	284 (3)	167 (11*)
60 Gy	1074 (4)	1042 (15)	1011 (23)	965 (28)	816 (18)	533 (10)	280 (10)	176 (10*)
57 Gy	1077 (5)	1044 (30)	1004 (35)	944 (31)	798 (31)	492 (9)	262 (13)	151 (9*)
Number censored								
74 Gy	0	24	22	26	107	280	200	114
60 Gy	0	28	16	23	121	265	243	94
57 Gy	0	28	10	25	115	275	221	98

Dearnaley et al, Lancet Oncol, 2016; 17: 1047-1060

Hipofrakcjonowanie w RT raka stercza

OS

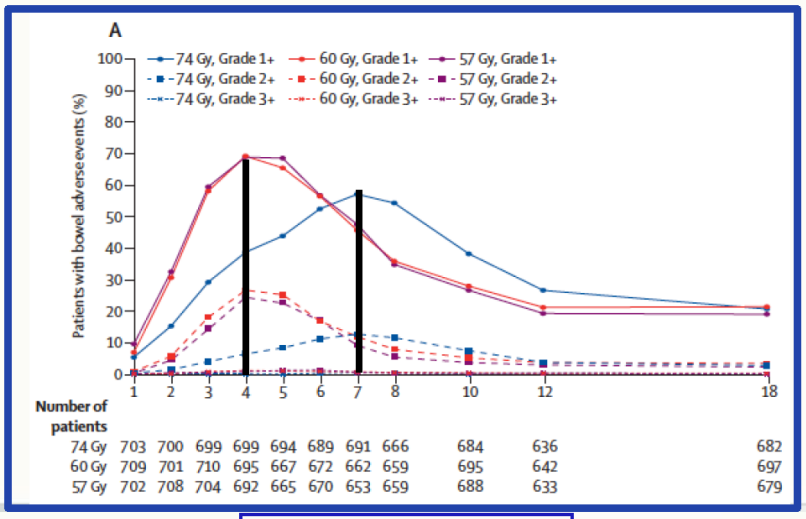


Number at risk (events)								
74 Gy	1065 (6)	1045 (13)	1025 (11)	996 (13)	889 (23)	585 (10)	337 (9)	201 (7*)
60 Gy	1074 (8)	1049 (6)	1035 (11)	1011 (10)	896 (14)	608 (10)	339 (4)	224 (10*)
57 Gy	1077 (7)	1053 (9)	1041 (7)	1021 (18)	910 (17)	606 (14)	336 (5)	217 (10*)
Number censored								
74 Gy	0	14	7	18	94	281	238	127
60 Gy	0	17	8	13	105	274	259	111
57 Gy	0	17	3	13	93	287	256	114

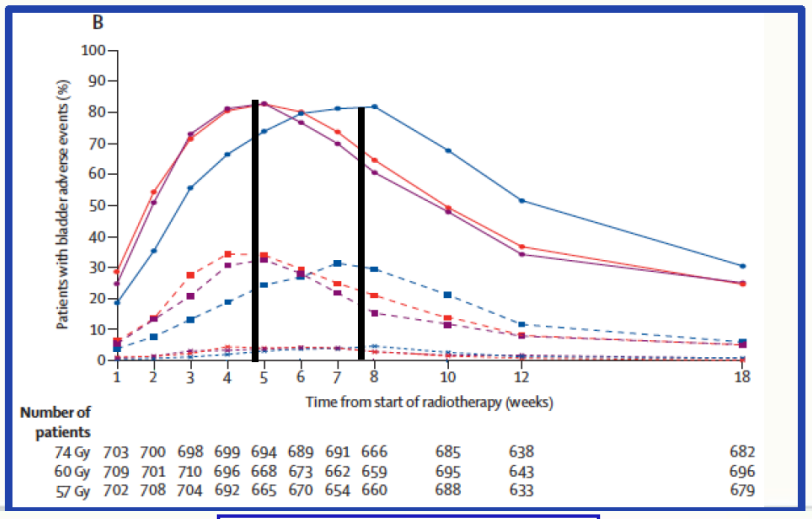
Dearnaley et al, Lancet Oncol, 2016; 17: 1047-1060

Hipofrakcjonowanie w RT raka stercza

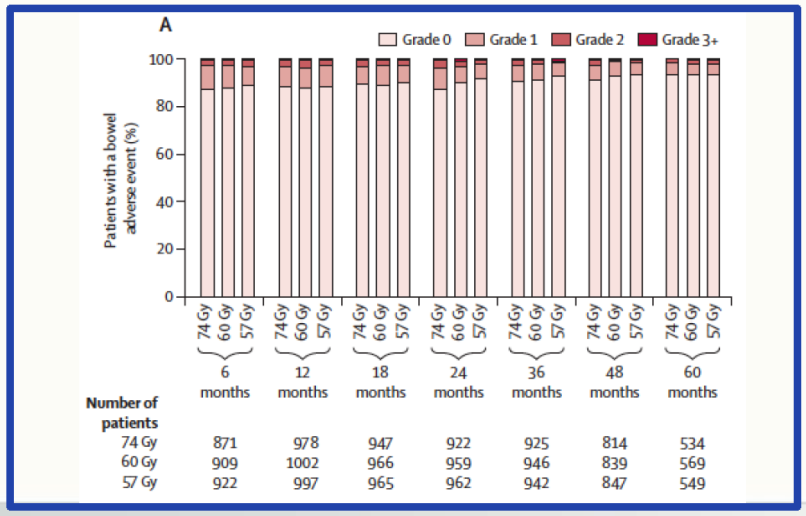
Acute Bowel toxicity



Acute Bladder toxicity

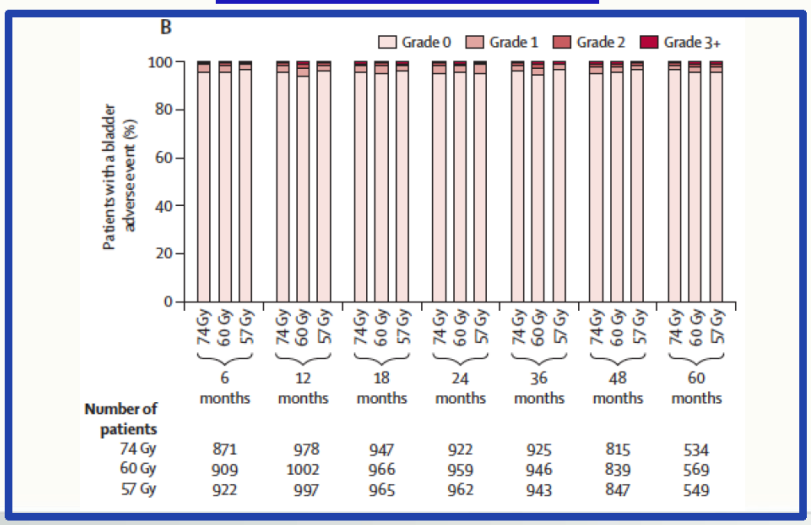


Late Bowel toxicity



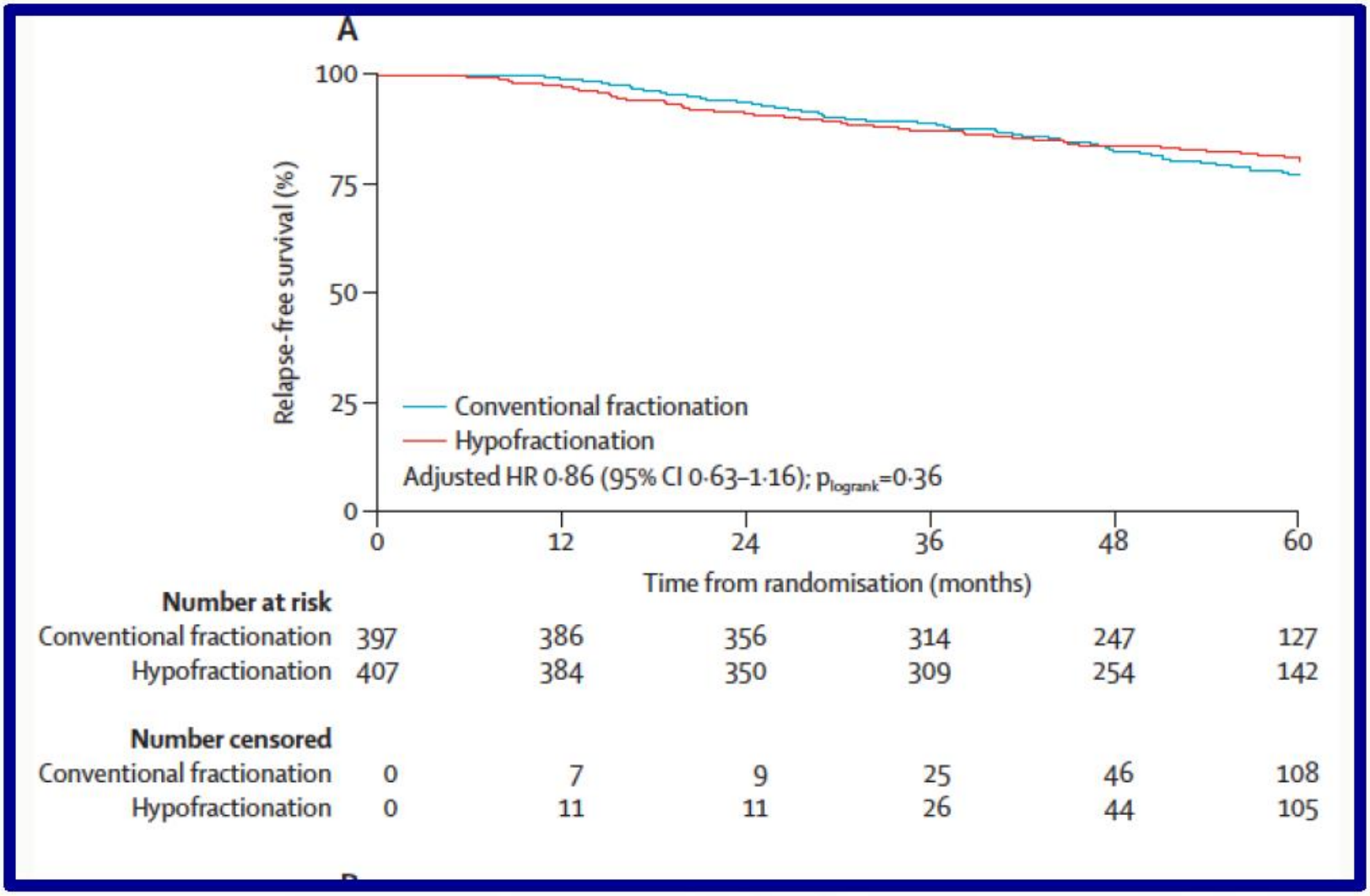
Dearnaley et al, Lancet Oncol, 2016; 17: 1047-1060

Late Bladder toxicity



Dearnaley et al, Lancet Oncol, 2016; 17: 1047-1060

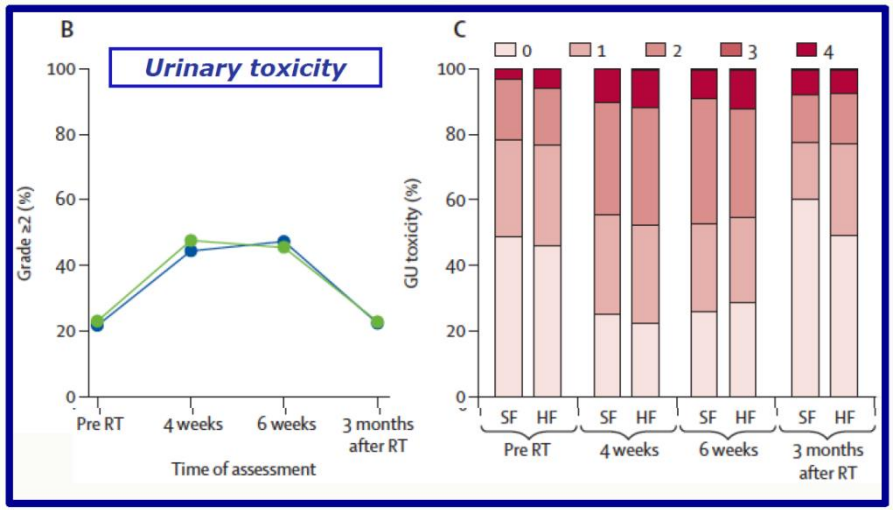
Hipofrakcjonowanie w RT raka stercza

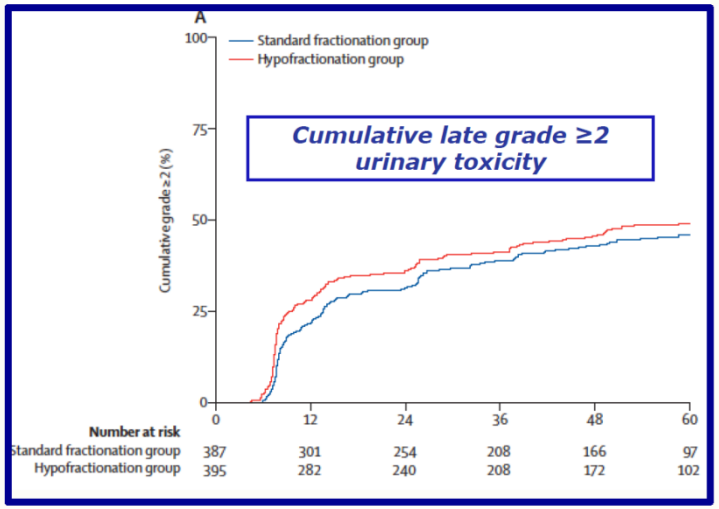


Number at risk						
Conventional fractionation	397	386	356	314	247	127
Hypofractionation	407	384	350	309	254	142
Number censored						
Conventional fractionation	0	7	9	25	46	108
Hypofractionation	0	11	11	26	44	105

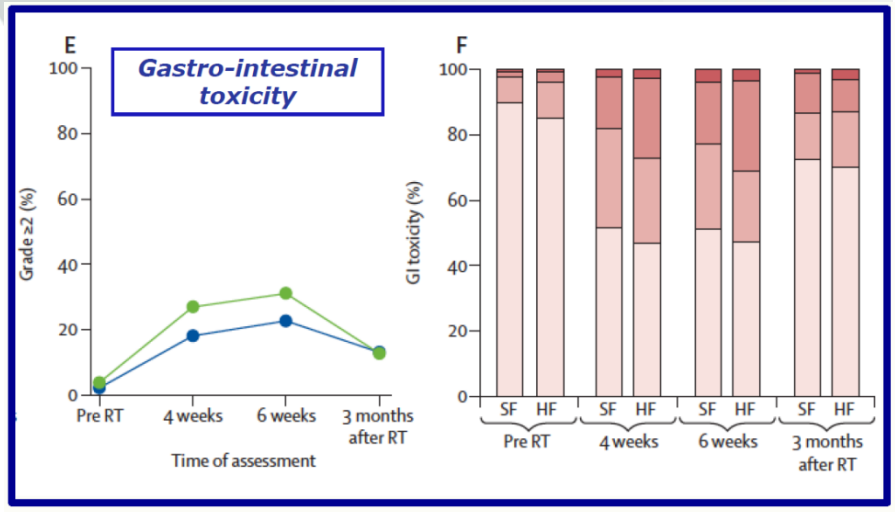
Incrocci et al, Lancet Oncol, 2016; 17: 1061-1069

Hipofrakcjonowanie w RT raka stercza

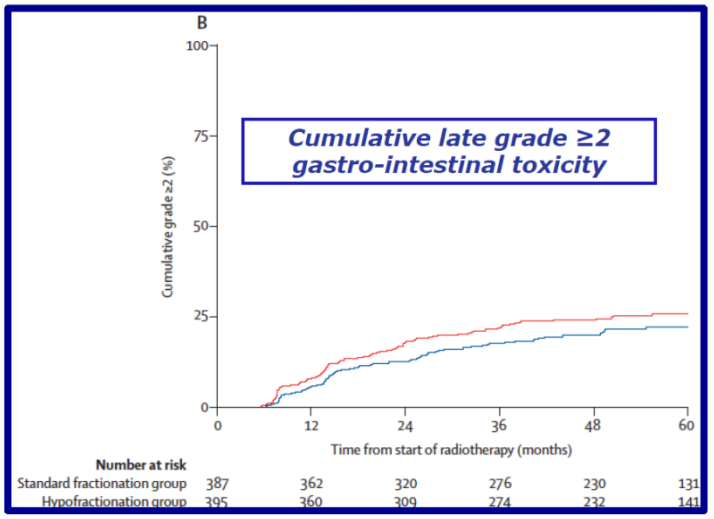




Aluwini et al, Lancet Oncol, 2016; 17:464-474

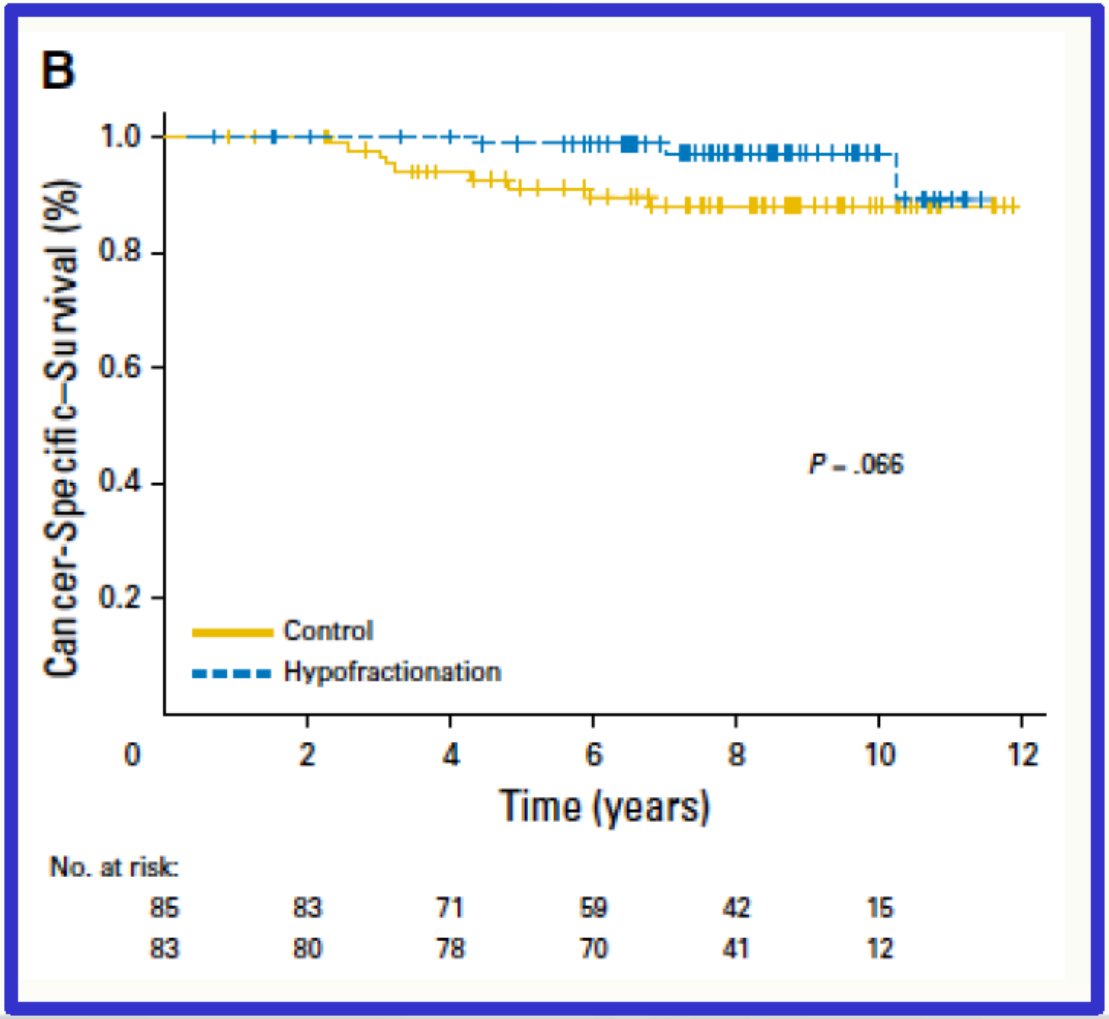


Aluwini et al, Lancet Oncol, 2015; 16:274-283



Aluwini et al, Lancet Oncol, 2016; 17:464-474

Hipofrakcjonowanie w RT raka stercza



CSS

Arcangeli et al, JCO, 2017; DOI: 10.1200/JCO.2016.70.4189

Hipofrakcjonowanie w RT raka stercza - przeżycie bez późnych powikłań stopnia ≥2

(A – układ moczowy, B – przewód pokarmowy)

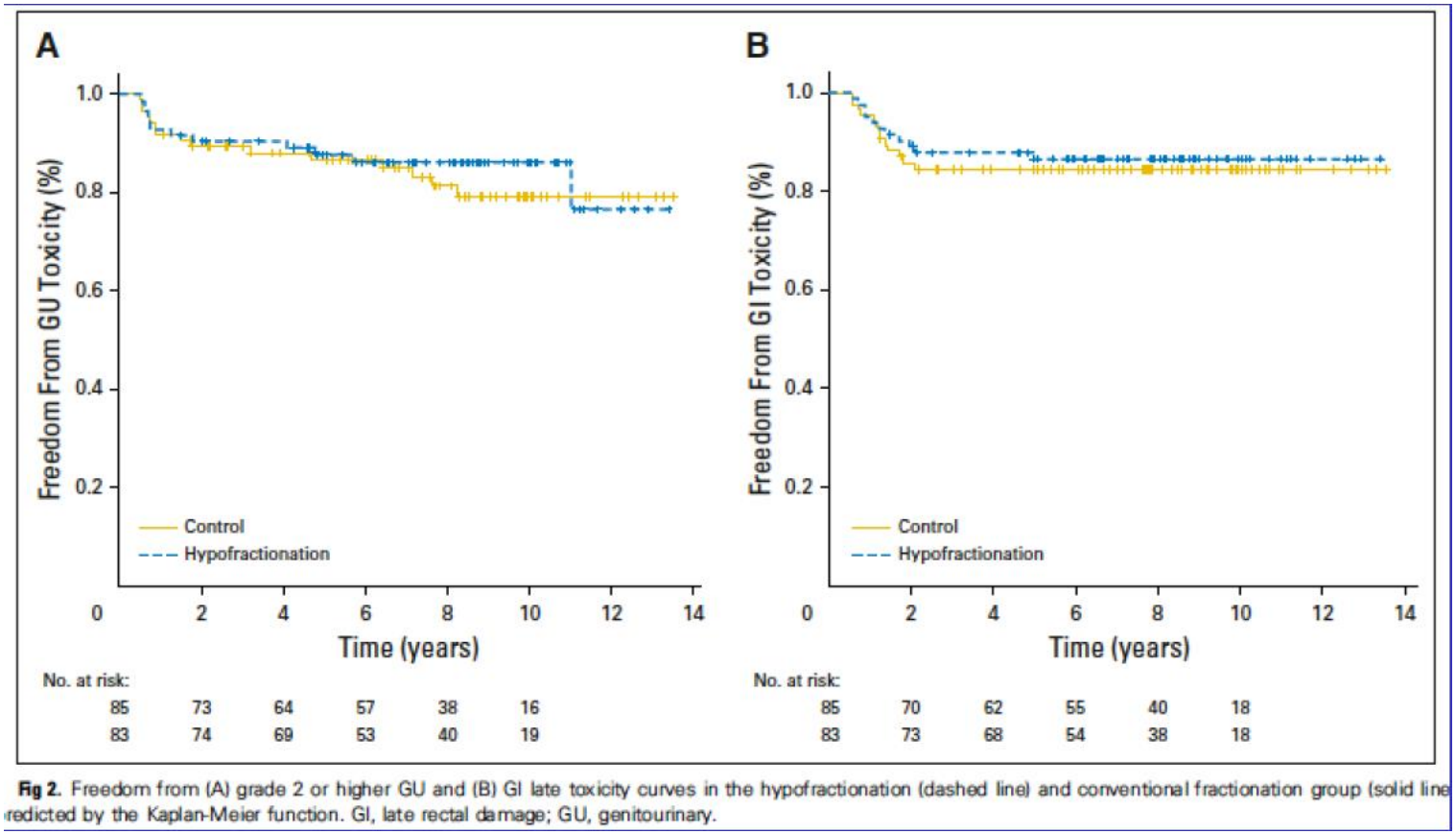


Fig 2. Freedom from (A) grade 2 or higher GU and (B) GI late toxicity curves in the hypofractionation (dashed line) and conventional fractionation group (solid line) predicted by the Kaplan-Meier function. GI, late rectal damage; GU, genitourinary.

Hipofrakcjonowanie w RT raka stercza

PHASE III STUDY OF HYPOFRACTIONATED, DOSE ESCALATION RT FOR HIGH RISK CANCER OF THE PROSTATE

PROSTATE CANCER STUDY 5 (PCS V)
A GROU-Q LED TRIAL

Tamim Niazi, M.D., Abdenour Nabid, M.D., Redouane Bettahar, M.D., Linda Suzanne Vincent, M.D., Andre-Guy Martin, M.D., Marjory Jolicoeur, M.D., Michael Yassa, M.D., Maroie Barkati, M.D., Levon Igidbashian, M.D., Boris Bahoric, M.D., Robert Archambault, M.D., Hugo Villeneuve, M.D., James M Tsui Ph.D., Md Mohiuddin, M.D.

High risk prostate Ca: PCS V

Patient Population:

329 HR Pca:
- T3a+
- PSA ≥ 20 ng/ul
- Gleason 8-10

RANDOMIZED 1:1

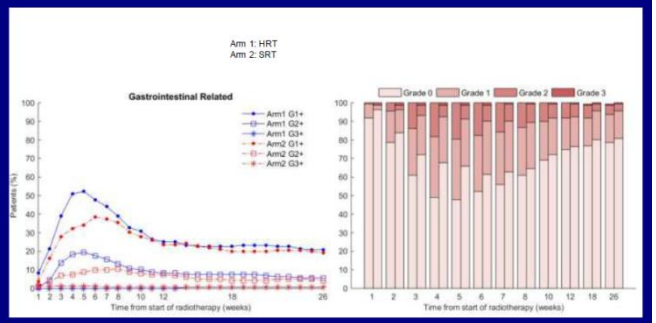
- N = 165 Strd fractionated (76Gy/38) + 28 m of LHRH agonist
- N = 164 Hypofractionated (68Gy/25) + 28 m of LHRH agonist

Primary end point:
Delayed GI and GU toxicity

Secondary end points:
PSA PFS
Metastases free survival
OS
DSS
QOL
Correlative science

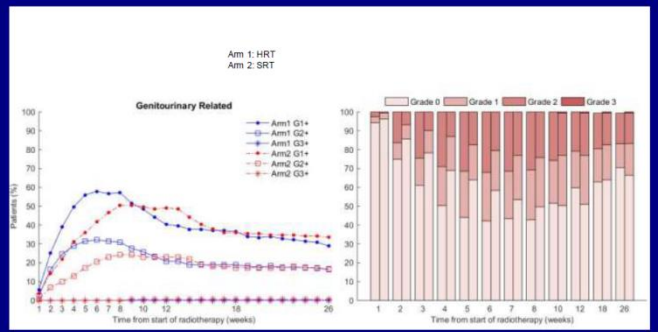
38 x 2 Gy = 76 Gy vs 25 x 2,72 Gy = 68 Gy

Acute Gastrointestinal Toxicity



GROU-Q Quebec GU Radiation Oncology Group

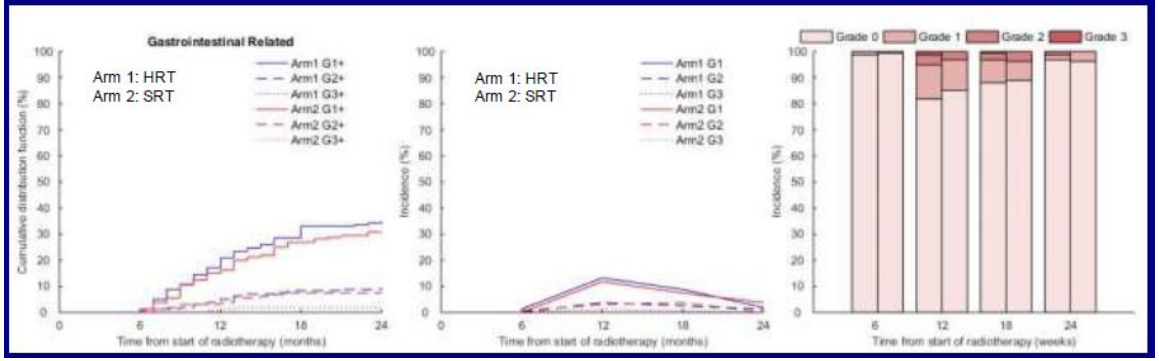
Acute GenitourinayToxicity



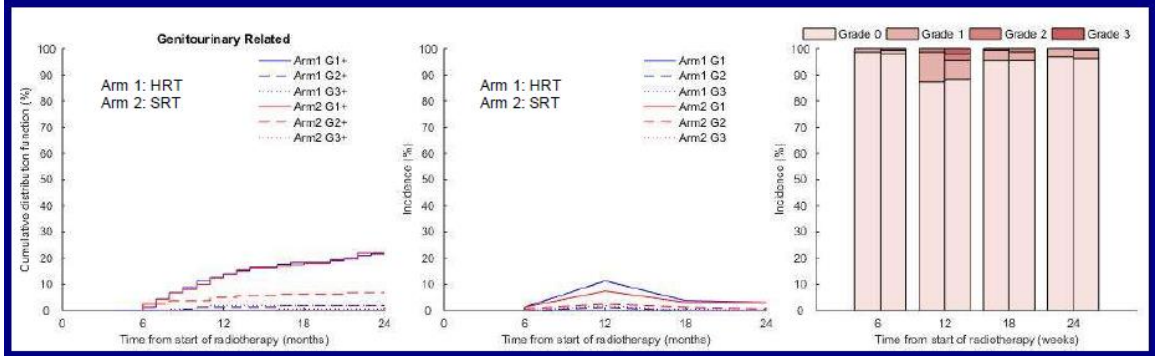
GROU-Q Quebec GU Radiation Oncology Group

Hipofrakcjonowanie w RT raka stercza

Late Gastrointestinal Toxicity



Late Genitourinary Toxicity



Late Toxicity

Late Toxicity	Total events	Arm 1	Arm 2	Arm 1 vs Arm 2 HR	(95% Wald CI)
Gastrointestinal Related					
Grade 1 or worse	104	55	49	1.2	(0.82-1.77)
Grade 2 or worse	27	15	12	1.32	(0.62-2.83)
Grade 3 or worse	3	3	0		
Grade 4 or worse	0				
Genitourinary Related					
Grade 1 or worse	69	34	35	0.98	(0.61-1.57)
Grade 2 or worse	14	3	11	0.26	(0.07-0.94)
Grade 3 or worse	4	1	3		
Grade 4 or worse	0				

Moderate hypo fractionated EBRT (68Gy/25) to high risk prostate cancer patients does not appear to carry more grade 3 or higher GI or GU acute and/or late toxicity.

Moderate hypo fractionated EBRT to a dose of 68Gy in 25 concomitant boost fractionation can safely be offered to M0 N0 high risk prostate cancer patients.

Schemat 25 x 2,72 Gy nie zwiększa ryzyka późnej toksyczności GI i GU ≥3 stopnia!!!

Czy należy eskalować dawkę RT?

Anatomical Patterns of Recurrence Following Biochemical Relapse in the Dose Escalation Era of External Beam Radiotherapy for Prostate Cancer

Zachary S. Zumsteg, Daniel E. Spratt, Paul B. Romesser, Xin Pei, Zhigang Zhang, Marisa Kollmeier, Sean McBride, Yoshiya Yamada* and Michael J. Zelefsky†

From the Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, New York, and the Department of Radiation Oncology, Cedars-Sinai Medical Center, Los Angeles, California (ZSZ)

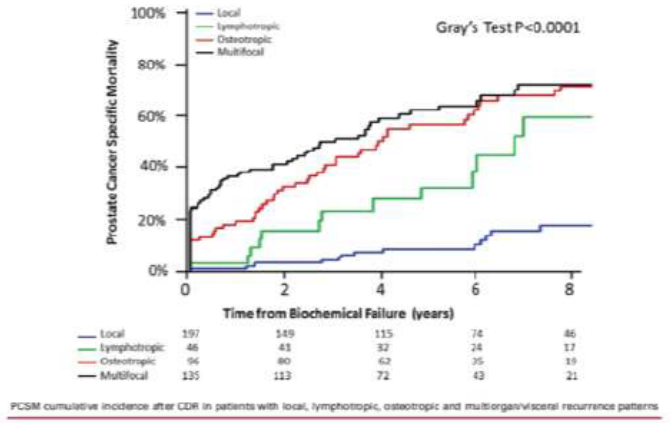
No indication how many patients had Bx

Local failure - determine clinically and probably **grossly under reported**

Retrospective analysis of EBRT 2,694 pts min 75.6 Gy (1991 to 2008)
LR : Bx or radiologicaly confirmed

Local failure is the most common first recurrence site in all risk groups 8-year cumulative incidence of

Low risk	3.5%
Interm Risk	9.8%
High Risk -	**14.6%**



PCSM cumulative incidence after CDR in patients with local, lymphotropic, osteotropic and multiorgan/visceral recurrence patterns

All failures contribute to increase in PCSM

THE JOURNAL OF UROLOGY® Vol. 194, 1624-1630, December 2015

Po eskalacji dawki >75 Gy – 8-letnia wznowa miejscowa w grupie

IR – **9,8**%, HR – **14,6**%

Wyniki eskalacji dawki RT poprzez łączenie teleRT z BT

RTC with LDR

ASCENDE RT

2486

Low-Dose-Rate Prostate Brachytherapy Is Superior to Dose-Escalated EBRT for Unfavorable Risk Prostate Cancer: The Results of the ASCENDE-RT Randomized Control Trial

S.L. Rodda,[1] S. Tyldesley,[1] M. Keyes,[2] M. McKenzie,[1] H.H. Pai,[3] G. Duncan,[1] J. Hamm,[1] and W.J. Morris[1]; [1]*BC Cancer Agency, Vancouver, BC, Canada,* [2]*British Columbia Cancer Agency, Vancouver, BC, Canada,* [3]*BC Cancer Agency, Surrey, BC, Canada*

IJROBPh 2016

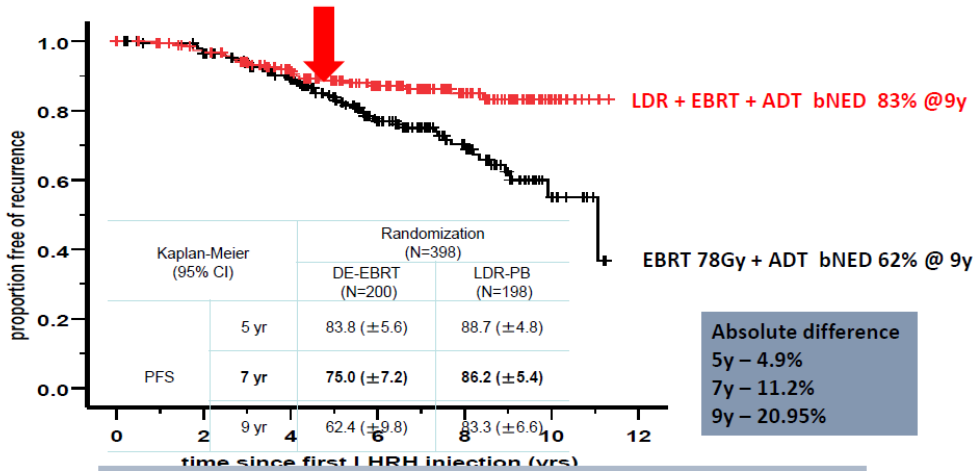
9-letnie przeżycie

bez wznowy

po EBRT+BT+ADT

– **83**%

ASCENDE RT - bPFS(Phoenix)at 5y – primary outcome



Kaplan-Meier (95% CI)		Randomization (N=398) DE-EBRT (N=200)	LDR-PB (N=198)
PFS	5 yr	83.8 (±5.6)	88.7 (±4.8)
	7 yr	75.0 (±7.2)	86.2 (±5.4)
	9 yr	62.4 (±9.8)	83.3 (±6.6)

Absolute difference
5y – 4.9%
7y – 11.2%
9y – 20.95%

- 5 years follow up is inadequate
- Brachytherapy Arm is superior with stable long term outcomes
- EBRT 10 y outcomes are poor

Zysk po dołączeniu BT w zakresie przeżycia bez wznowy po 5 latach – 4,9%, po 7 latach 11,2%, po 9 latach – **20,95**%

Eskalacja dawki EBRT + BT

Brachytherapy - **better OS?**

Survival Outcomes of Dose-Escalated External Beam Radiotherapy versus Combined Brachytherapy for Intermediate and High Risk Prostate Cancer Using the National Cancer Data Base

Arya Amini,* Bernard Jones, Matthew W. Jackson, Norman Yeh, Timothy V. Waxweiler, Paul Maroni, Brian D. Kavanagh and David Raben

From the Department of Radiation Oncology and Division of Urology, Department of Surgery (PM), University of Colorado School of Medicine, Aurora, Colorado

20,279 Pts cN0M0 pCa
US NCDB
2004 – 2006
Med FU 82 mo

EBRT - 71%
EBRT + PB boost 29%

12,617 IR,
7,662 HR

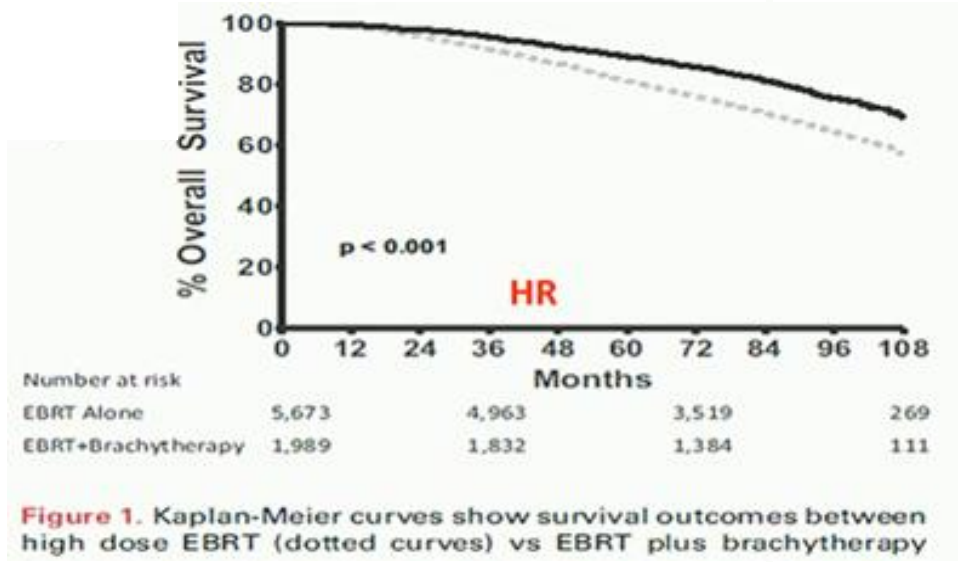


Figure 1. Kaplan-Meier curves show survival outcomes between high dose EBRT (dotted curves) vs EBRT plus brachytherapy

THE JOURNAL OF UROLOGY® Feb 2016

11-letnie OS po EBRT + BT w HR PCa – **80**%

Rola eskalacji dawki RT i czasu trwania ADT

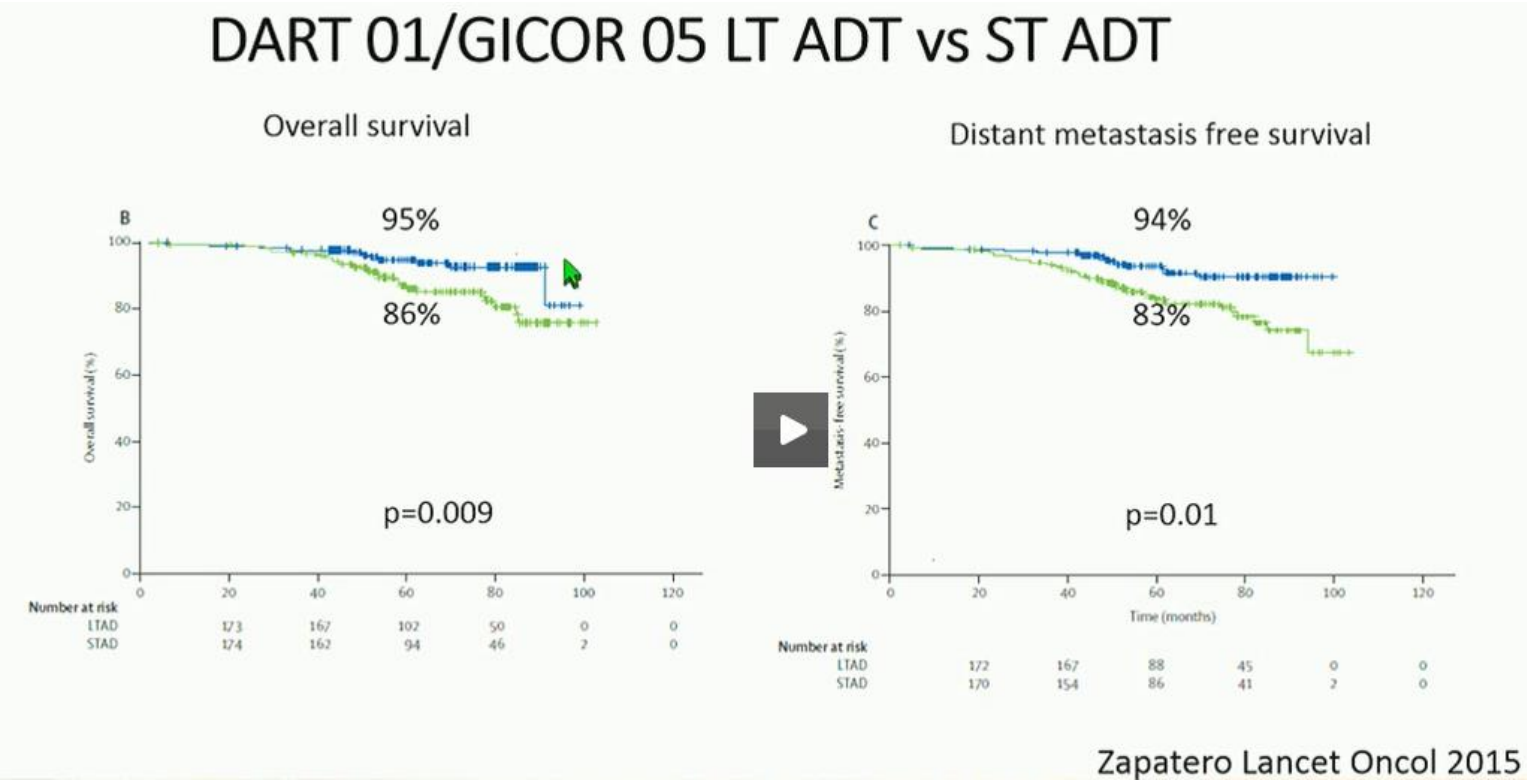
Wyniki badania TROG 03.04 RADAR

- Materiał: 1051 ch.
- Ocena ryzyka miejscowej progresji (LP)
- Dawka: 66 vs 70 vs **74 Gy vs HDR boost**
- Skumulowane ryzyko LP po 6,5 latach: 22%, 15%, 13% i 7%
- ADT: 6 mies. vs 18 mies.

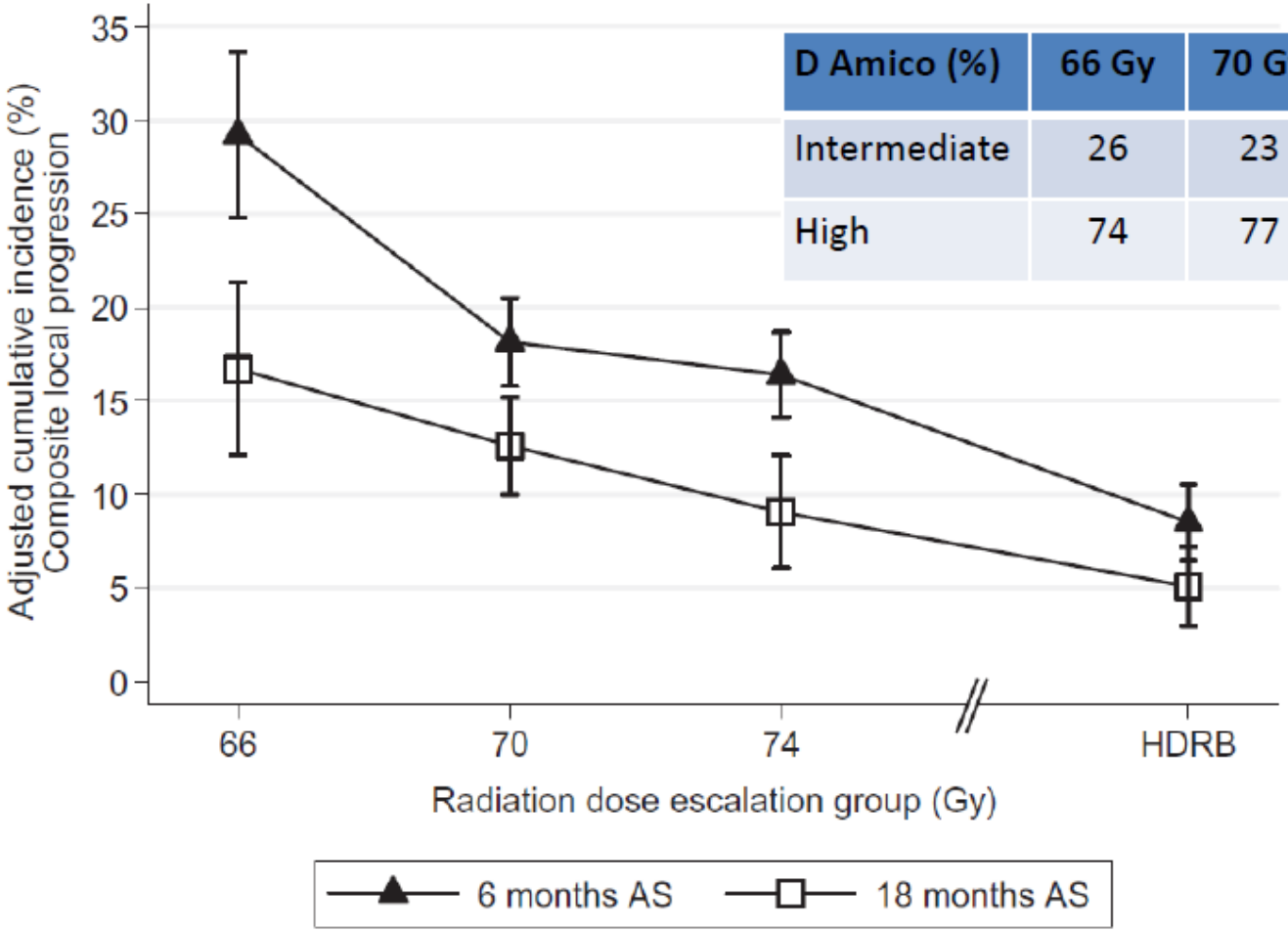
- Wnioski:
- Istotny statystycznie narastający wpływ wysokości dawki
- Istotny statystycznie wpływ wydłużenia ADT
- **Optymalny schemat - wysoka dawka RT (EBRT+BT) + długotrwała ADT**

Denham JW, Steigler A, Joseph D et al. Radiation dose escalation or longer androgen suppression for locally advanced prostate cancer? Data from the TROG 03.04 RADAR trial. Radiother Oncol 2015; 115: 301-307.

Rola dawki RT i czasu trwania ADT



Eskalacja dawki RT + wydłużona ADT wpływa na 5-letnie OS (**95**%) i 5-letnie przeżycie bez odległych przerzutów (**94**%)



D Amico (%)	66 Gy	70 Gy	74 Gy	HDRB
Intermediate	26	23	22	8
High	74	77	78	92

TROG 03.04 RADAR Trial

Denham et al, R&O, 2015

Optymalny schemat - wysoka dawka RT (EBRT+BT) + długotrwała ADT

Wyniki EBRT+BT+ADT w HR PCa

5-letnie bRF przeżycie po IMRT/IGRT– **92%- 95%**

Azelie C et al. Oncology 2012, Zelefsky M et al. IJROBPh 2011

7-8-letnie bRF przeżycie po EBRT+BT – **70-98%**

Fang, L. C. *et al. Int. J. Radiat. Oncol. Biol. Phys. 2011*
Vargas, C. *et al. Prostate Cancer Prostatic Dis. 2006*

10-letnie bRF przeżycie po EBRT+BT – **85%-87%**

Grimm p et al. BJUI 2012, Bittner N et al. Brachytherapy 2013

8-9-letnie przeżycie bez LR – **80%-85%**

Rodda SI et al. IJROBPh 2016, Zumsteg ZS et al. JUrol 2015

5-letnie OS i 5-letnie przeżycie bez DM – 95%, 94%

Zapatero Lancet Oncology 2015

10-letnie CSS i OS po EBRT+BT: **90-93% i 78%-82%**

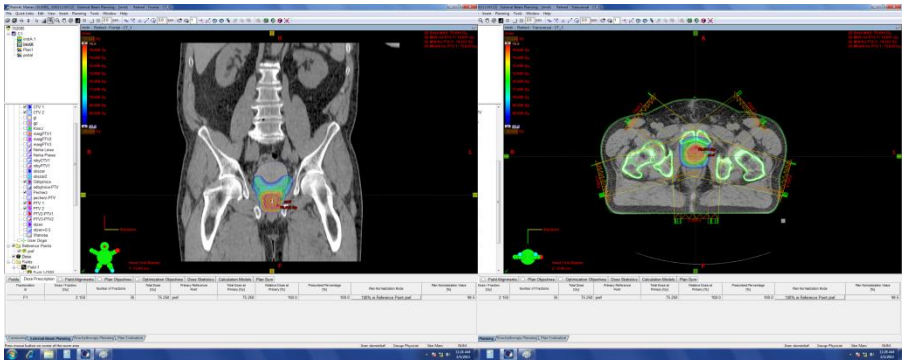
Dattoli M et al. J Oncol. 2010, Prada P et al. Radiat Oncol 2012, Arcangeli et al. IJROBPh 2012, Amini A et al. Jurol 2016

15-letnie CSS: **80-82%,** OS **73%**

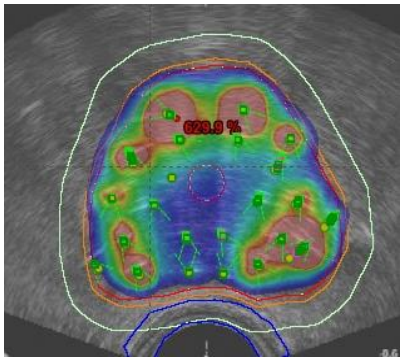
Nguyen QN Cancer. 2013

Protokół RT u chorych IR i HR-PCa w Zakładzie Teleradioterapii w Łodzi

- TRUS, TK jamy brzusznej, wieloparametryczny RM
- Implantacja metalicznych znaczników
- Planowanie RT w 3D na podstawie TK
- Fuzja obrazów RM i TK



- MAB przez 2 mies:
- T3 - IMRT/IGRT 2.6 Gy x 27 fx = 70.2 Gy **[NTD=82,23 Gy]** (BED – 192 Gy, *α/β = 1.5 Gy*)
  T2a,T2b, T2c – EBRT/BT - 37,5 Gy/15 fr. /15 Gy **[NTD=113,6 Gy]** (BED – 265 Gy, *α/β = 1.5 Gy*)
- jednoczesna MAB
- Uzupełniająca ADT analogiem LHRH-
  do 24 mies.(HR), 6 mies. (IR)



Protokół RT u chorych IR i HR-PCa w Zakładzie Teleradioterapii w Łodzi

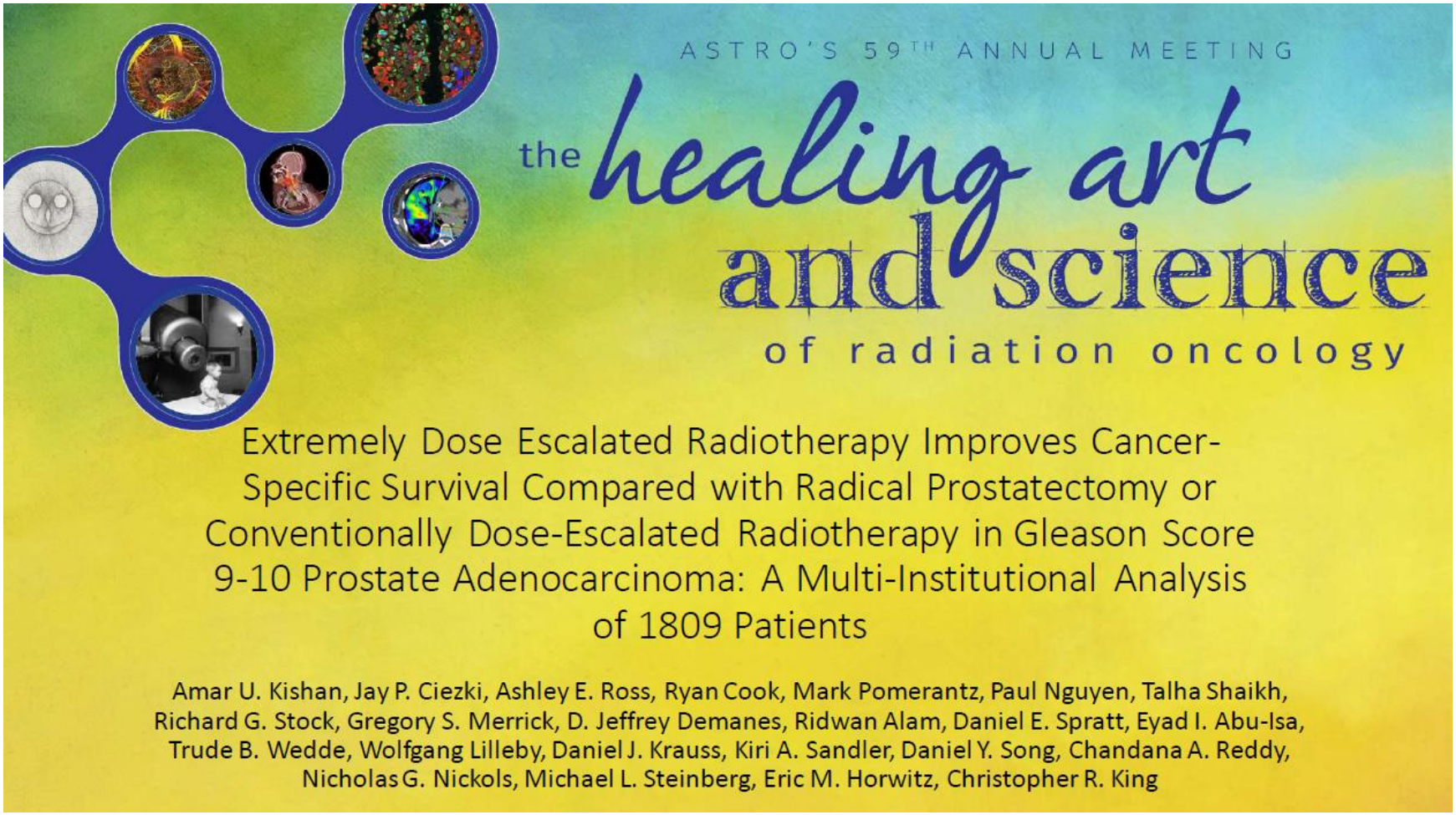
- Sunnybrook Odette Cancer Centre in Toronto, has adopted a boost policy of 15 Gy HDR as a single fraction, combined with EBRT to a dose of 37.5 Gy in 15 fractions over 3 weeks. This protocol began as a Phase II clinical trial for patients with intermediate risk prostate cancer in 2005.

- At a median follow-up of 6.2 years, the 5-year biochemical disease-free survival (Phoenix definition) is over 97% (95% confidence intervals: 93-99%).

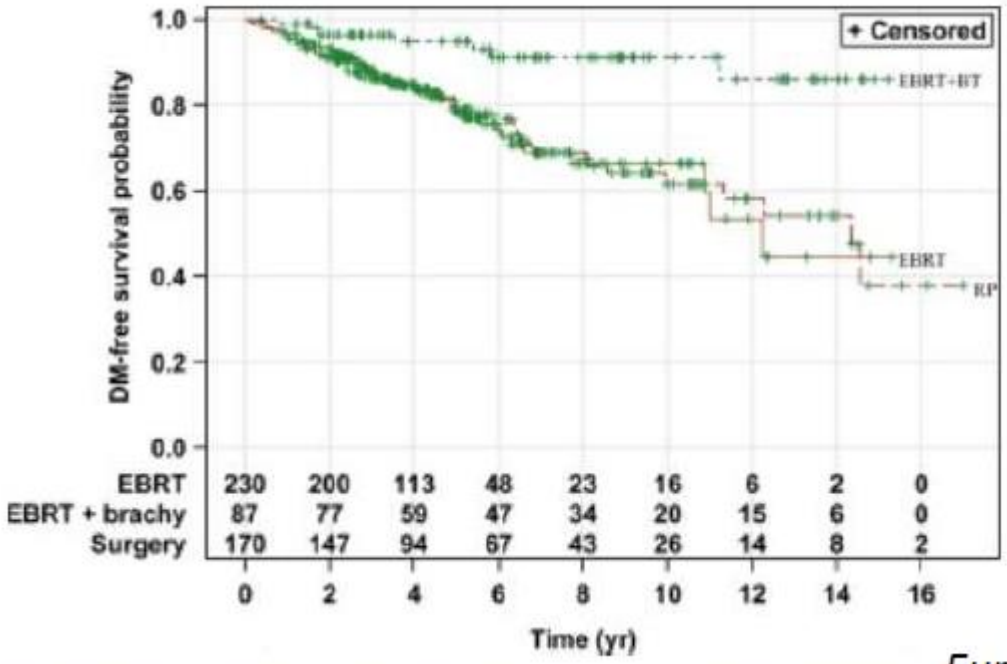
- Clinical efficacy and toxicity are similar to that of previous protocol of HDR delivered in two fractions of 10 Gy and an external beam dose of 45 Gy in 25 fractions. It is, however, more acceptable to patients and makes more efficient use of resources.

- The protocol has been widely adopted across Canada, the United Kingdom, and in many U.S. centers. A single 15 Gy has become the standard HDR boost dose in current Radiation Therapy Oncology Group clinical trials (RTOG 0924 and RTOG 1115). It remains well tolerated with a Grade 3 or higher late toxicity rate of < 5%.

RP czy RT u chorych HR-Pca (ASTRO 2017)



RP czy RT u chorych HR-Pca (ASTRO 2017)

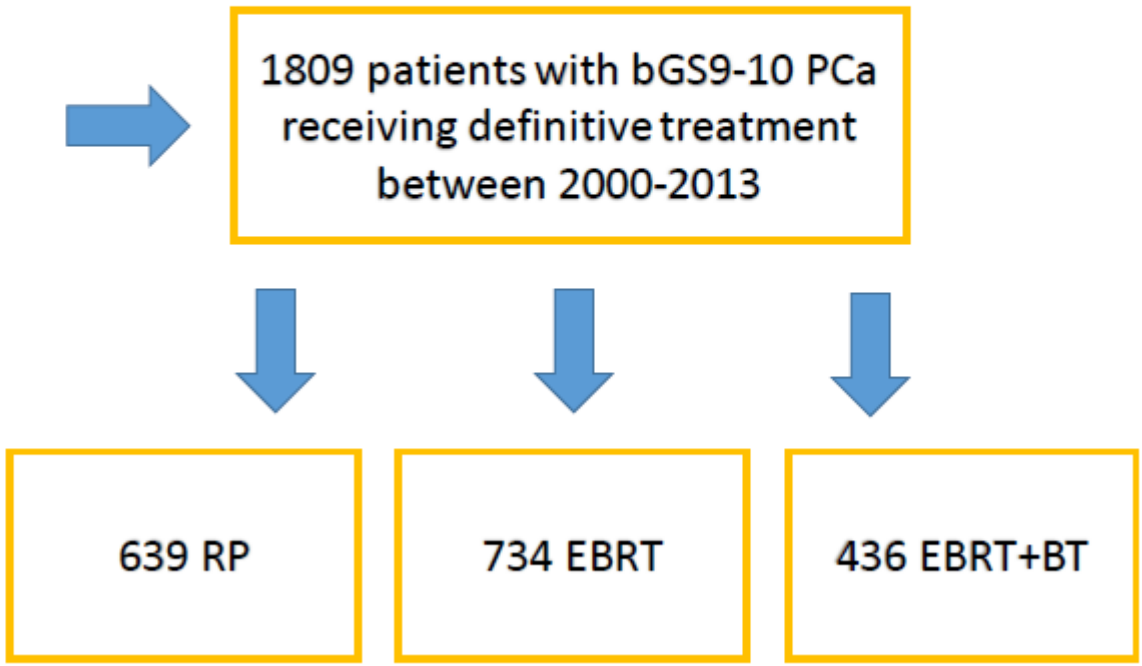


Eur Urol. 2017

Grupa 487 chorych (i.Gl 9-10) znacząco korzystniejsze DMFS po EBRT+BT z krótkotrwałą ADT w stosunku do EBRT i RP, jednakże w tej grupie jedynie 87 przypadków

RP czy RT u chorych HR-Pca (ASTRO 2017)

Participating Institutions
UCLA
CET
Cleveland Clinic
Johns Hopkins
Dana-Farber
Fox Chase
Mount Sinai
Wheeling Hospital
University of Michigan
Oslo University Hospital
William Beaumont
Greater Los Angeles VA



RP czy RT u chorych HR-Pca (ASTRO 2017)

	RP (n=639, 35%)	EBRT (n=734, 41%)	EBRT+BT (n=436, 24%)	PS-Adjusted SMD*	p-value
CLINICAL CHARACTERISTICS					
Age, mean, median (years)	61.0 61.2 (39-77.1)	67.7 68 (39.7-98)	67.5 68.0 (48-83)	0.127	EBRT vs. RP p<0.005 EBRT + BT vs. RP p<0.005 EBRT+BT vs. EBRT p>0.5
Initial PSA, mean, median (ng/mL)	11.26 6.9 (0.4-378.6)	21.5 9.93 (0.4-525.5)	14.8 9.6 (0.1-273.5)	0.006	EBRT vs. RP p<0.005 EBRT + BT vs. RP p<0.005 EBRT+BT vs. EBRT p<0.005
Biopsy Gleason Score					
9	613 (95.9%)	686 (93.5%)	398 (91.3%)	0.048	EBRT vs. RP p<0.005 EBRT + BT vs. RP p<0.005 EBRT+BT vs. EBRT p>0.15
10	26 (4.1%)	48 (6.5%)	38 (8.7%)		
Clinical Tumor Stage (%)					
1c	327 (51.2%)	212 (28.9%)	148 (33.9%)	0.05	EBRT vs. RP p<0.005 EBRT + BT vs. RP p<0.005 EBRT+BT vs. EBRT p<0.005
2	230 (36.0%)	300 (40.8%)	195 (44.7%)		
3a	36 (5.6%)	103 (14.0 %)	63 (14.4%)		
3b	21 (3.3%)	75 (10.2%)	17 (3.9%)		
4	24 (3.8%)	44 (6.0%)	3 (3.0%)		

PS, propensity score; propensity score weighting performed on the basis of age, ln(iPSA), bGS, and cT stage.
SMD, standardized mean difference

RP czy RT u chorych HR-Pca (ASTRO 2017)

	RP	EBRT	EBRT+BT	p-value
Radiotherapy Patients				
Total dose in EQD_2, median		74.3 (65-81.4)	91.5 (75.8-131.4)	p<0.005
Upfront ADT usage		657 (89.5%)	403 (92.4%)	p>0.5
Duration of ADT, median		21.9 (1-160)	12.0 (1-100)	p<0.05
Pelvic nodal irradiation		299 (40.7%)	320 (73.4%)	p<0.05
RP Patients				
Neoadjuvant systemic therapy	120 (19%)			
Adjuvant RT	56 (8.7%)			
Adjuvant systemic therapy	72 (11.3%)			
All Patients				
Local salvage	218 (34.1%)	18 (2.5%)	4 (0.1%)	EBRT vs. RP p<0.005 EBRT + BT vs. RP p<0.005 EBRT+BT vs. EBRT p>0.05
Systemic salvage	155 (24.1%)	89 (12.1%)	24 (5.5%)	EBRT vs. RP p<0.005 EBRT + BT vs. RP p<0.005 EBRT+BT vs. EBRT p<0.005

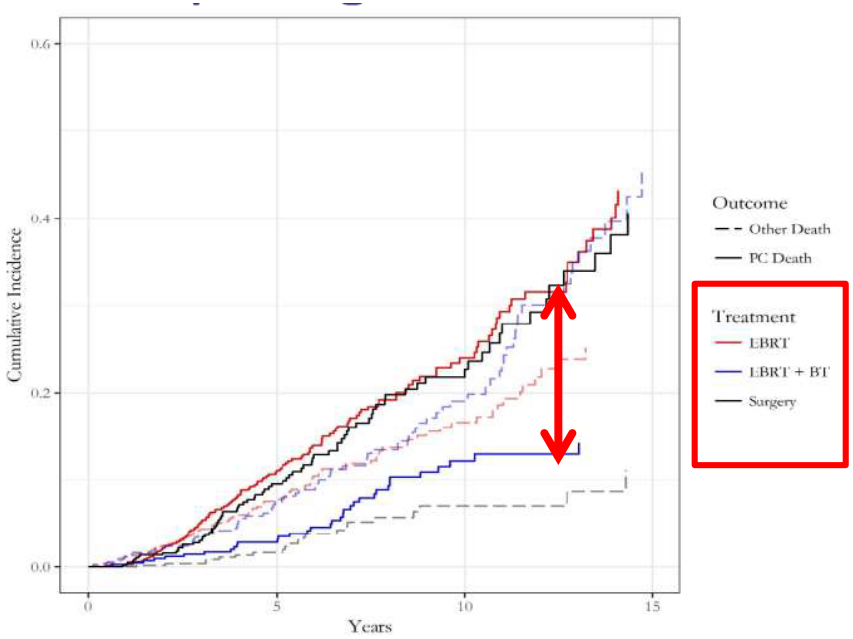
RP czy RT u chorych HR-Pca (ASTRO 2017)

Parameter	Comparison	CHR(95% CI)	p-value
Distant Metastasis			
Unadjusted	EBRT vs. RP	0.99 (0.80, 1.23)	.9
	EBRT + BT vs. RP	**0.29 (0.18, 0.47)**	**<.001**
	EBRT + BT vs. EBRT	**0.29 (0.18, 0.46)**	**<.001**
Propensity score-adjusted	EBRT vs. RP	0.90 (0.70, 1.14)	.4
	EBRT + BT vs. RP	**0.27 (0.17, 0.43)**	**<.001**
	EBRT + BT vs. EBRT	**0.30 (0.19, 0.47)**	**<.001**
Prostate Cancer Specific Mortality			
Unadjusted	EBRT vs. RP	1.08 (0.81,1.44)	.6
	EBRT + BT vs. RP	**0.42 (0.24,0.74)**	**.003**
	EBRT + BT vs. EBRT	**0.39 (0.23,0.67)**	**<.001**
Propensity score-adjusted	EBRT vs. RP	0.92 (0.67,1.26)	.6
	EBRT + BT vs. RP	**0.38 (0.21,0.68)**	**.001**
	EBRT + BT vs. EBRT	**0.41 (0.24,0.71)**	**.002**

Adjustments are for ln(iPSA), age, T stage, and Gleason score

Analiza regresji Coxa

RP czy RT u chorych HR-Pca (ASTRO 2017)

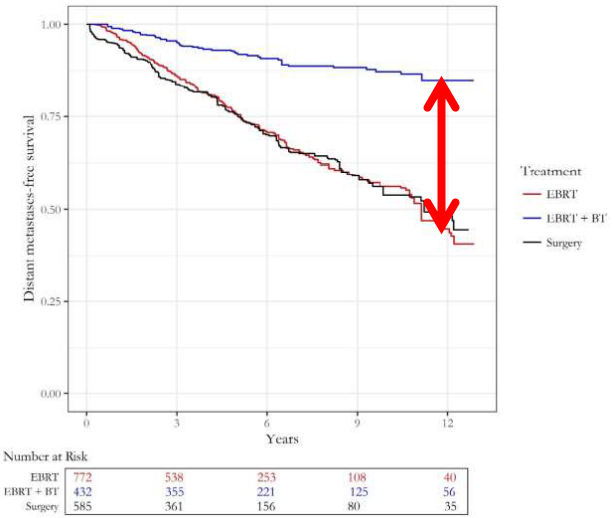


Unadjusted	SHR(95% CI)	p-value
EBRT vs. RP	1.13 (0.98, 1.30)	.1
EBRT + BT vs. RP	**0.39 (0.20, 0.76)**	**.005**
EBRT + BT vs. EBRT	**0.34 (0.18, 0.67)**	**.002**

PS-Adjusted	SHR(95% CI)	p-value
EBRT vs. RP	1.05 (0.88, 1.24)	.6
EBRT + BT vs. RP	**0.38 (0.19, 0.73)**	**.004**
EBRT + BT vs. EBRT	**0.36 (0.18, 0.70)**	**.003**

Zgon z powodu PCa

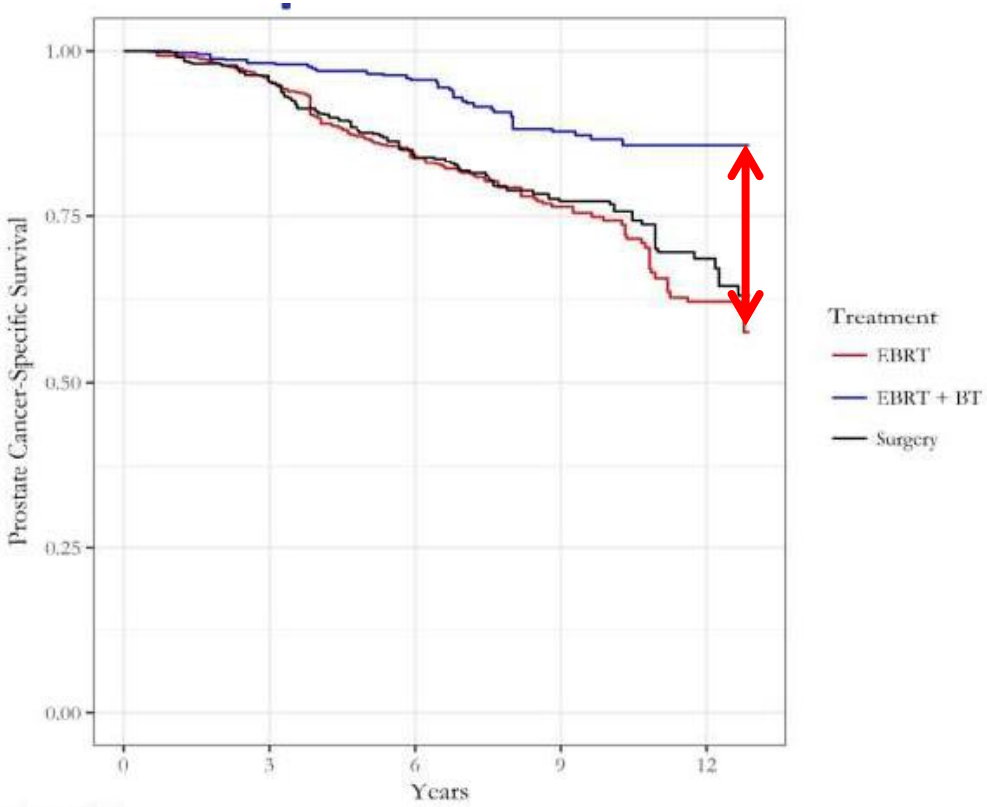
DMFS



RP czy RT u chorych HR-Pca (ASTRO 2017)

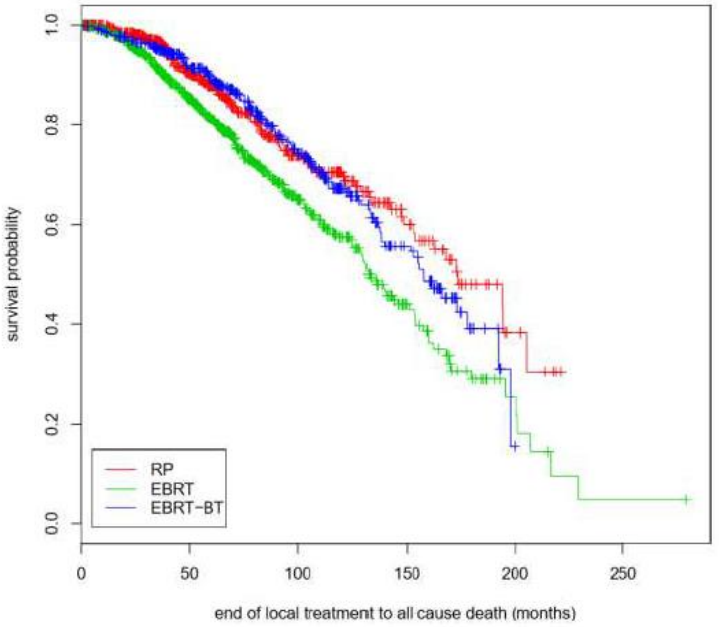
Prostate cancer specific survival

OS!!!



Number at Risk

EBRT	764	583	312	143	58
EBRT + BT	428	362	234	125	57
Surgery	586	407	181	98	48



Kaplan-Meier curve (courtesy of Fang-I Chu, PhD)

RP czy RT u chorych HR-Pca (ASTRO 2017)

Posumowanie wyników:

- **Chorzy poddani EBRT+BT i otrzymujący ≥ 78 Gy oraz ≥ 24 mies. ADT uzyskali istotną korzyść w zakresie DM i PCSM w porównaniu z poddanymi RP lub EBRT z długotrwałą ADT;**

- **5-letnia skumulowana śmiertelność z powodu raka stercza wyniosła w grupie EBRT+BT - 3%, w grupie RP – 10%, w grupie EBRT – 11%**

  10-letnia śmiertelność odpowiednio: 12%, 23% i 24%

- **<u>W dodatkowej analizie brak wpływu metody leczenia na OS</u>**

- *Brak informacji o schorzeniach współistniejących*

- *Brak analizy toksyczności leczenia*

RP – wyniki w grupie HR - (EAU 2014)

Table 9.2: Overall survival (OS) and cancer-specific survival (CSS) rates for high-risk localized and locally advanced PCa treated with RP as first treatment in a multimodal approach

Reference	n	Time span	OS			CSS			PSA-free survival		
			5-yr	10-yr	15-yr	5-yr	10-yr	15-yr	5-yr	10-yr	15-yr
GS 8-10 at biopsy											
Donohue et al. (2006) (50)	246	1983-2004	-	-	-	-	-	-	51	39	-
Bastian et al. (2006) (56)	220	1982-2004	-	-	-	-	-	-	40	27	-
Yossepowitch et al. (2008) (57)	401	1985-2005	-	-	-	96	88	-	-	-	-
Stephenson et al. (2009) (36)	702	1987-2005	-	-	-	-	84	66	-	-	-
Walz et al. (2010) (58)	269	1987-2005	-	-	-	-	-	-	35	24	-
PSA > 20 ng/mL											
Zwergel et al. (2007) (59)	275	1986-2005	87	70	58	93	83	71	53	25	25
Magheli et al. (2007) (60)	265	1984-2005	-	-	-	-	-	-	47	33	-
Yossepowitch et al. (2008) (57)	441	1985-2005	-	-	-	97	91	-	-	-	-
Stephenson et al. (2009) (36)	726	1987-2005	-	-	-	-	90	78	-	-	-
Walz et al. (2010) (58)	370	1987-2005	-	-	-	-	-	-	40	26	-
Gontero et al. (2011) (55)	712	1987-2005	90	73	-	95	89	-	63	48	-
cT3a											
Ward et al. (2005) (44)	841	1987-1997	90	76	53	95	90	79	58	43	38
Carver et al. (2006) (61)	176	1983-2003	-	-	-	94	85	76	48	44	-
Hsu et al. (2007) (45)	200	1987-2004	96	77	-	99	92	-	60	51	-
Freedland et al. (2007) (62)	62	1987-2003	-	-	-	98	91	84	62	49	49
Yossepowitch et al. (2008) (57)	243	1985-2005	-	-	-	96	89	-	-	-	-
Xylinas et al. (2009) (63)	100	1995-2005	-	-	-	90	-	-	45	-	-
Stephenson et al. (2009) (36)	254	1987-2005	-	-	-	-	85	62	-	-	-
Walz et al. (2010) (58)	293	1987-2005	-	-	-	-	-	-	52	44	-

CSS = cancer-specific survival; n = number of patients; PSA = prostate-specific antigen; RP = radical prostatectomy.

10-letnie bPFS: 24-51%

10-letnie OS: 70-77%

10-letnie CSS: 83-92%

RP – wyniki w grupie vHR - (EAU 2014)

Table 9.3: Overall survival (OS), cancer-specific survival (CSS) rates for very-high-risk PCa treated with RP as first treatment in a multimodal approach

Reference	n	Time span	OS			CSS			PSA-free survival		
			5-yr	10-yr	15-yr	5-yr	10-yr	15-yr	5-yr	10-yr	15-yr
cT3b-T4											
Johnstone et al. (2006) (66)	72	1995-2001	73	-	-	88	-	-	-	-	-
Joniau et al. (2012) (64)	51	1989-2004	88	71	-	92	92	-	53	46	-
Any T and N1											
Messing et al.(2006) (68) (*with vs without ADT)	98	1988-1993		55* 36 (11.5 yr)			85* 51 (11.5 yr)			53* 14 (11.5 yr)	
Schumacher et al. (2008) (72)	122	1989-2007	83	52	42	85	60	45	14	3	-
Da Pozzo et al. (2009) (74)	250	1988-2002	-	-	-	89	80	-	72	53	-
Engel et al. (2010) (69)	688	1988-2007	84	64	-	95	86	-	-	-	-
Steuber et al. (2011) (70)	108	1992-2004	79	69	-	84	81	-	-	-	-
Briganti et al. (2011) (73)	364	1988-2003	85	60	-	90	75	-	-	-	-

CSS = cancer-specific survival; n = number of patients; PSA = prostate-specific antigen; RP = radical prostatectomy.

10-letnie bPFS: 3-53%

10-letnie OS: 36-71%

10-letnie CSS: 51-92%

RP w HR PCa

Table 4 | Large retrospective series of radical prostatectomy in high-risk patients

Study	*n*	Definition of high-risk	PCSS	Comments on population	Adjuvant therapy
Briganti *et al.* (2012)[76]	1,366	PSA >20 ng/ml or cT3 or biopsy Gleason ≥8	10-year PCSS 91% 10-year PCSS 98% in organ-confined vs 88% in non-organ confined disease	57% with cT3 75% with pT3–4 Adjuvant RT in 66.4% of organ-confined vs 16.8% of non-organ confined disease	48% received therapy (ADT and/or RT) 8.2% adjuvant RT 29.7% adjuvant ADT 10.2% adjuvant RT+ADT
Boorjian *et al.* (2011)[75]	1,238	PSA >20 ng/ml or cT3 or biopsy Gleason ≥8	10-year PCSS 92%	33% with cT3-4	40% received therapy (6.9% adjuvant RT; 29.5% adjuvant ADT; 4.1% both RT and ADT)
Stephenson *et al.* (2009)[67]	1,962	PSA >20 ng/ml or cT3 or biopsy Gleason ≥8	10-year PCSS 92% 15-year PCSS 81%	Large study, high-risk represented 17% of overall population	Not reported
Ward *et al.* (2005)[77]	841	cT3	10-year PCSS 90% 15-year PCSS 79%	18% with Gleason ≥8 Mean PSA 10.2 (4.7–23.7) ng/ml	51% received adjuvant RT; 16% received adjuvant ADT
Yossepowitch *et al.* (2008)[78]	1,359* 938‡	8 high-risk definitions compared	10-year PCSS 93% per D'Amico 10-year PCSM 92% per NCCN	10-year cumulative incidence varied by definition (3–11%)	30–39% received ADT and/or RT within 5 years, but almost all at BCR or salvage; no adjuvant ADT and only 31 cases of adjuvant RT
Eggener *et al.* (2011)[68]	631 modelling; 726 validation cohort	High-risk *per se* not defined, but reports on subset of patients with Gleason ≥8	10-year PCSS 82–87% for Gleason >8	PCSS by age: 70–79 years: 82% 60–69 years: 87% <60 years: 85%	Not reported
Spahn *et al.* (2010)[69]	712	PSA >20 ng/ml	10-year estimated PCSS 89.8%	44% with cT3-4 20% with Gleason ≥8	Adjuvant RT varied by number of additional risk factors (11.9–21.6%); adjuvant ADT similarly varied based on additional risk factors (35.4–84.1%)
Zwergel *et al.* (2007)[70]	275	PSA >20 ng/ml	10-year PCSS 83%	75% also pT3 49% with Gleason ≥8	129/275 (47%) immediate ADT (almost all before 2000, when practice patterns changed at this institution) Survival did not differ between immediate vs deferred ADT 2/275 adjuvant RT (<1%)

*Based on D'Amico definition. ‡Based on NCCN definition. Abbreviations: ADT, androgen-deprivation therapy; BCR, biochemical recurrence; NCCN, National Comprehensive Cancer Network; PCSM, prostate cancer-specific mortality; PCSS, prostate cancer-specific survival; PSA, prostate-specific antigen; RT, radiotherapy; vs, versus.

48-51% chorych otrzymuje uzupełniające leczenie:

uzupełniającą RT (6,9%-51%),
ADT (16%-84,1%)
lub RT+ADT (4,1%-39%)

RP w grupie wysokiego ryzyka progresji (HR) EAU 2014

RP +PLND (ryzyko N+ 15-40%) u wybranych chorych z zachowaną ruchomością stercza, bez nacieku zwieracza cewki, z małą objętością guza

Kwalifikacja do RP powinna być wynikiem wielospecjalistycznej konsultacji

RP ma miejsce w leczeniu chorych HR, chociaż jest wciąż przedmiotem kontrowersji !!!!

cT3 w 13%-27% pT2

Ale… 33,5-66% SM+, 7,7-49% pN(+)

Konieczna diagnostyka TK, RM miednicy

Konieczne najwyższe kwalifikacje chirurga

Chory musi być poinformowany o możliwości koniecznego uzupełniającego leczenia (RT/ADT)

Wyniki pooperacyjnych badań H-P (R1, liczne SM+, pT3b, neuro- i angioinwazja, N+….)

1. Dwanaście węzłów chłonych biodrowo-zasłonowych prawych, bez przerzutu raka (0/12).
2. Jeden z pięciu węzłów chłonnych biodrowo-zasłonowych lewych, z przerzutem raka (1/5).
3. Prostata o wymiarach 5x5x4,5cm wraz z obustronnymi kikutami nasieniowodów i pęcherzykami nasiennymi.

Histologicznie:
Adenocarcinoma prostatae, wg Gleasona 7(4+3).
Grade group 3.
Rak zajmuje rozlegle oba płaty prostaty, nacieka na obwodzie "torebkę" narządu i w kilku wycinkach ją przekracza ("extraprostatic extension").
W wycinkach ze strony lewej gruczoły krokowego utkanie raka zbiega się z linią cięcia operacyjnego na obszarze 0,3mm.
Widoczne są cechy angio i neuroinwazji.
Rak nie nacieka wolnej części pęcherzyków nasiennych.
pT3a N1 R1 LV1

NUMER BADANIA: **80044-046**

Rodzaj materiału:
1-prostata i pęcherzyki nasienne,
2-węzły biodrowo zasłonowe prawe,
3-węzły biodrowo zasłonowe lewe,

Wynik
1. Rak gruczołowy stercza. Wskaźnik Gleasona 7 (4+3).
Utkanie raka stwierdza się w wycinkach z płata prawego i lewego. Nowotwór nacieka torebkę stercza i tkanki miękkie poza nią (neuroinwazja) – margines chirurgiczny tkanek miękkich poza torebką stercza bez nacieku raka. Ponadto naciek raka obejmuje pęcherzyki nasienne (obustronnie). Naciek raka dochodzi do marginesu chirurgicznego od strony wierzchołka stercza. Margines chirurgiczny od strony szyi pęcherza bez nacieku raka.
2. Węzeł chłonny bez przerzutów raka.
3. Węzeł chłonny bez przerzutów raka.

pT3bN0 ICD O 3: M8140/3

Wiek: 59 **Płeć: M** **PESEL**

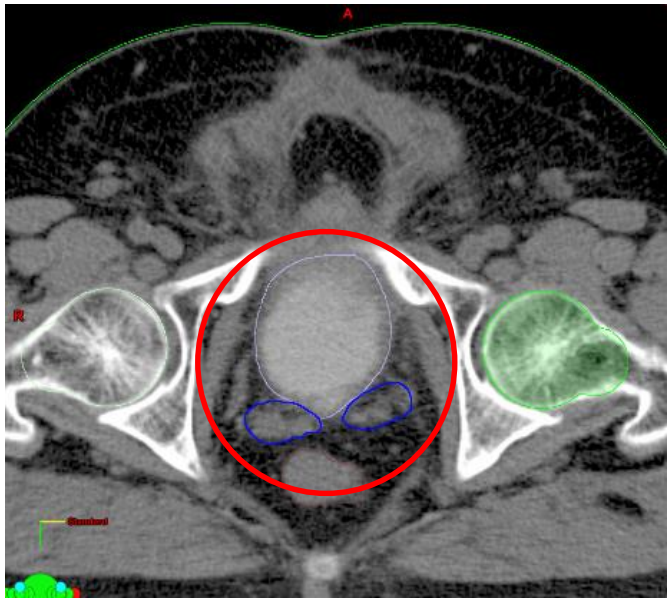
Dane kliniczne (początek, umiejscowienie, dzień cyklu miesiączkowego, radioterapia, chemio- i hormonoterap...):
Rak stercza wysokiego ryzyka – PSA 15 ng/ml.

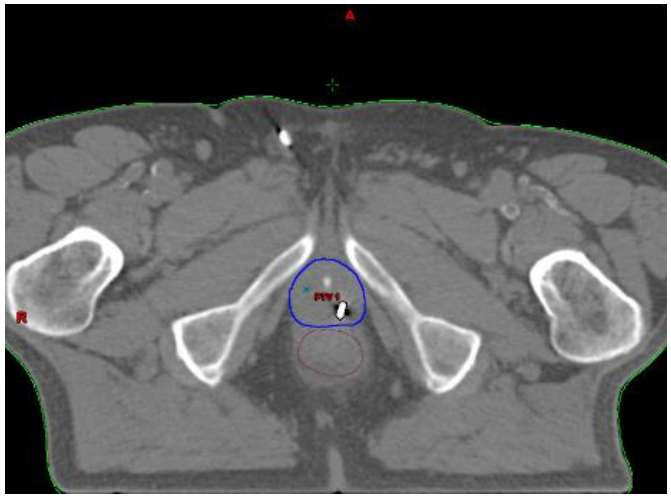
Rozpoznanie histopatologiczne:
Gruczoł krokowy o wym. 5x4,5x4,2 cm. Pęcherzyk nasienny prawy wraz z nasieniowodem o wymiarach 4x2,5x1,5 cm. Pęcherzyk nasienny lewy wraz z nasieniowodem o wymiarach 4x3x1 cm.
W obydwu płatach gruczołu krokowego obecny jest naciek raka gruczołowego zrazikowego, obejmujący po około 30% powierzchni ocenianych wycinków po obu stronach. Obecne są cechy neuroinwazji. Brak jednoznacznych i bezspornych cech angioinwazji. Obwodowe linie chirurgicznego odcięcia tkanek oraz stożek bez nacieku raka. Powierzchnia pęcherzowa nacieczona przez raka. Linie odcięcia nasieniowodów bez nacieku raka.
Węzły chłonne biodrowe i zasłonowe strony prawej bez przerzutów raka.
Węzły chłonne biodrowe i zasłonowe strony lewej bez przerzutów raka.
Margines od strony pęcherza moczowego bez nacieku raka.

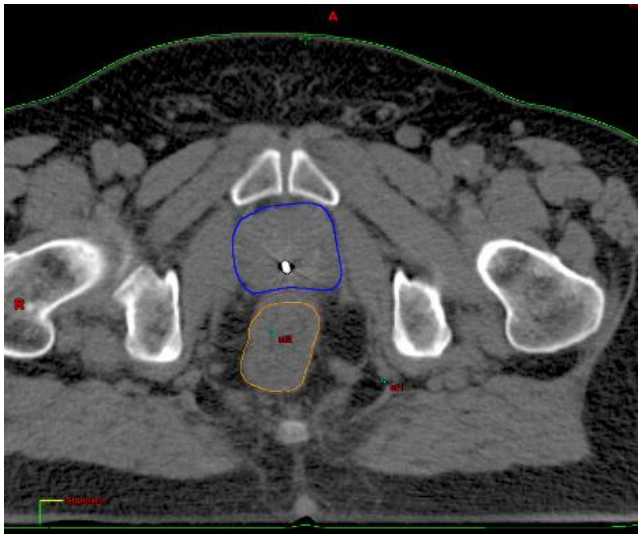
ROZPOZNANIE KOŃCOWE:
Rak gruczołowy zrazikowy gruczołu krokowego, Gleason score 8 (4+4), grade group 4, obustronnie naciekający pęcherzyki nasienne, pT3b N0

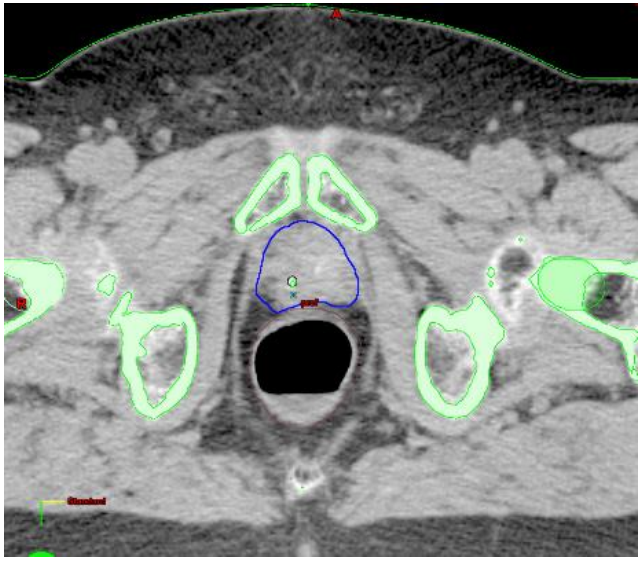
pooper. stężenie PSA 1,1 ng/ml

Polska rzeczywistość jest daleka od idealnego świata międzynarodowych rekomendacji – chorzy po „radykalnej” prostatektomii kierowani do uzupełniającej RT – „cancer sparing surgery”









Problem kliniczny

Pacjenci z czynnikami ryzyka mają po radykalnej prostatektomii 40-70% ryzyko wznowy biochemicznej w czasie 5 lat obserwacji

Jeśli nie zostanie włączone leczenie, u 2/3 chorych z tej grupy dojdzie do przerzutów odległych

Połowa chorych z pooperacyjnym PSADT <12 mies. umiera w czasie 10-13 lat obserwacji

Stephenson AJ, Scardino PT, Kattan MW, Pisansky TM, Slawin KM, Klein EA, et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. J Clin Oncol (2007) 25(15):2035–41. doi:10.1200/JCO.2006.08.9607

Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. JAMA (1999) 281(17):1591–7. doi:10.1001/jama.281.17.1591

Pound CR, Partin AW, Eisenberger MA et al: Natural history of progression after PSA elevation following radical prostatectomy. JAMA 1999; **281:** 1591.

Albertsen PC, Hanley JA, Penson DF et al: Validation of increasing prostate specific antigen as a predictor of prostate cancer death after treatment

of localized prostate cancer with surgery or radiation. J Urol 2004; **171:** 2221.

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Review – Prostate Cancer
Editorial by XXX on pp. x–y of this issue

Surgery Versus Radiotherapy for Clinically-localized Prostate Cancer: A Systematic Review and Meta-analysis

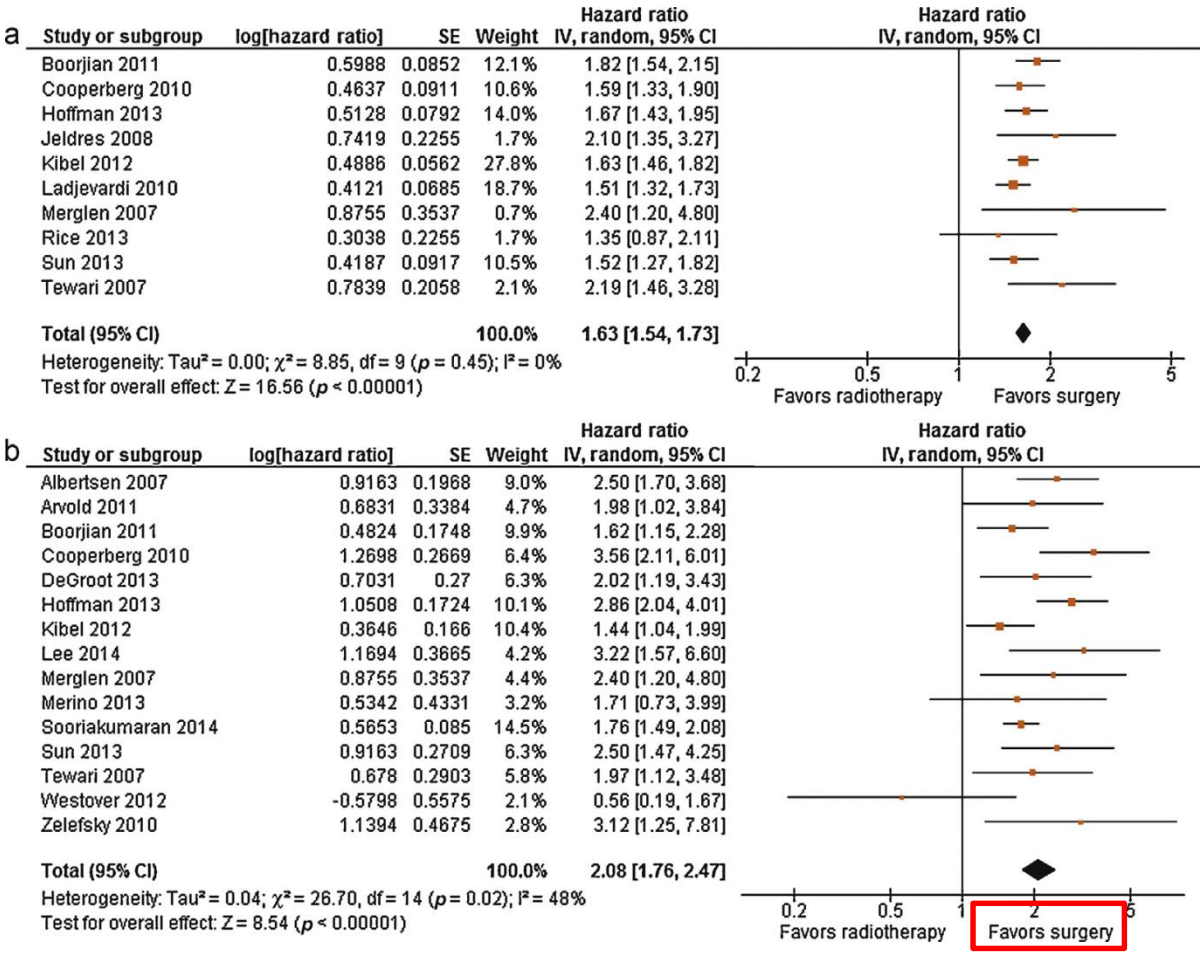
Christopher J.D. Wallis [a,b,c], Refik Saskin [c,d], Richard Choo [e], Sender Herschorn [a,b], Ronald T. Kodama [a,b], Raj Satkunasivam [a,b], Prakesh S. Shah [c,f,g], Cyril Danjoux [h], Robert K. Nam [a,b,c,]*

Śmiertelność ogólna i specyficzna dla raka wyższe po RT vs RP

Badanie poddane metodologicznej krytyce

The risk of overall (10 studies, aHR 1.63, 95% confidence interval 1.54–1.73, p < 0.00001; I2 = 0%) and prostate cancer-specific (15 studies, aHR 2.08, 95% confidence interval 1.76–2.47, p < 0.00001; I2 = 48%) mortality were higher for patients treated with radiotherapy compared with those treated with surgery.

118 830 patients



Zarzuty wobec publikacji Wallis'a (B. De Bari, A. Zietman, P. Poortmans)

- Skala Newcastle-Ottawa zastosowana przy selekcji badań nieprawidłowa (*systematic bias*)
- W 11/19 badań RT nie podana dawka napromieniania
- Rozgraniczenie prac RT „przed i po r. 2005" nie może być surogatem wysokości dawki
- W materiale z rejestrów nie uwzględniono faktu zastosowania uzupełniającej RT po RP a ma to wpływ na efekt końcowy w postaci śmiertelności z powodu raka stercza lub ogólnego przeżycia
- Z pracy nie mogą być wyciągnięte żadne wiarygodne wnioski dotyczące „wyższości" RP nad RT

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Letter to the Editor

Prostatectomy vs radiation therapy for prostate cancer: The (still) unsolved dilemma

To the Editor

Recently, Wallis et al. published a meta-analysis that suggests the superiority of prostatectomy over radiation therapy (RT) for clinically localized prostate cancer [1]. The topic has, for a long time, been of crucial interest in uro-oncology. Unfortunately, this meta-analysis shares the same methodological limits of other meta-analyses having addressed this same issue in the past.

The Newcastle-Ottawa Scale (NOS) [2] used for the preliminary evaluation of the included study's bias could not be considered adapted, as a threshold score distinguishing between 'good' and 'poor' quality studies is still lacking in NOS, as is clearly stated in the NOS website [2]. Thus, the initial criteria, even if reasonable, introduce a systematic bias in the preliminary selection of the studies.

In Table 1 in the study of Wallis et al., authors summarize the study's characteristics: it is clear that it is impossible to conclude anything about the effectiveness of RT when 11/19 studies give no information about the total delivered dose, a factor which is known to influence the outcome [3]. Anyway, looking at enrollment periods, it is very likely that the total delivered doses would nowadays be considered insufficient. Moreover, the criterion "before vs after 2005" cannot be a surrogate of the dose levels, as only recently we acquired the strong evidence of the impact of dose escalation on treatment outcomes, based on randomized trials.

More than 80% of the data are taken from registries: their importance in driving the therapeutic choices of physicians is well known, as are the potential major limits of the data quality within them, a factor which strongly influences the final quality of the interpretation of the results.

Randomized and retrospective studies already showed the impact of adjuvant and/or salvage RT in improving disease free survival and overall survival [4,5]. The information on the proportion of patients having received RT after prostatectomy is lacking in this meta-analysis: this is another important limit of the studied data, and hence of the results.

Finally, this meta-analysis presents a clear confounding by severity bias: likely, in the considered patients, the severity of the disease acts as a confounding factor, as prostatectomy will likely be proposed easier to patients with a good performance status and/or earlier stage disease [6].

In conclusion, any analysis aiming at obtaining results based on weak data will be affected by major methodological biasses, leading to a correspondently weak conclusion. Only the ongoing prospective randomized trials will answer the yet unsolved question addressed by the study of Wallis et al. In just a few months, the British ProtecT randomized trial (NCT02044172) will report on large numbers of men managed by high quality surgery or radiation therapy or by active surveillance, with a median follow-up of over ten years. Whatever the ultimate results of that trial, it will have far greater meaning and influence, making this meta-analysis completely redundant. Until that point in time, RT +/− hormonal therapy should be considered a valid first-choice curative option in the therapeutic approach to prostate cancer.

References

[1] Wallis CJD et al. Surgery versus radiotherapy for clinically-localized prostate cancer: a systematic review and meta-analysis. Eur Urol 2015. http://dx.doi.org/10.1016/j.eururo.2015.11.010.
[2] Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. 2011. Available at <http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp>. Accessed online on 13/02/2016.
[3] Zaorsky NG, Palmer JD, Hurwitz MD, Keith SW, Dicker AP, Den RB. What is the ideal radiotherapy dose to treat prostate cancer? A meta-analysis of biologically equivalent dose escalation. Radiother Oncol 2015 Jun;115:295–300.
[4] Arcangeli S, Ramella S, De Bari B, Franco P, Alongi F, D'Angelillo RM. A cast of shadow on adjuvant radiotherapy for prostate cancer: a critical review based on a methodological perspective. Crit Rev Oncol Hematol 2016 Jan;97:322–7.
[5] Freedland SJ, Rumble RB, Finelli A, Chen RC, Slovin S, Stein MN, et al. Adjuvant and salvage radiotherapy after prostatectomy: American Society of Clinical Oncology clinical practice guideline endorsement. J Clin Oncol 2014 Dec 1;32:3892–8.
[6] Salas M, Hofman A, Stricker BHC. Confounding by indication: an example of variation in the use of epidemiologic terminology. Am J Epidemiol 1999;149:981–3.

Berardino De Bari
Radiation Oncology Department, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland

Anthony Laurence Zietman
Radiation Oncology Department, Massachusetts General Hospital (MGH), Boston, USA

Philip Poortmans
Radiation Oncology Department, Radboud university medical center, Nijmegen, The Netherlands

Received 16 February 2016
Received in revised form
28 March 2016
Accepted 28 March 2016

Available online 4 June 2016

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer

F.C. Hamdy, J.L. Donovan, J.A. Lane, M. Mason, C. Metcalfe, P. Holding,

This article was published on September 14, 2016, at NEJM.org.

CONCLUSIONS

At a median of 10 years, prostate-cancer–specific mortality was low irrespective of the treatment assigned, with no significant difference among treatments. Surgery and radiotherapy were associated with lower incidences of disease progression and metastases than was active monitoring. (Funded by the National Institute for Health Research; Current Controlled Trials number, ISRCTN20141297; ClinicalTrials.gov

Table 1. Prostate-Cancer Mortality, Incidence of Clinical Progression and Metastatic Disease, and All-Cause Mortality, According to Randomized Treatment Group.

Variable	Active Monitoring (N=545)	Surgery (N=553)	Radiotherapy (N=545)	P Value*
Prostate-cancer mortality				
Total person-yr in follow-up	5393	5422	5339	
No. of deaths due to prostate cancer†	8	5	4	
Prostate-cancer–specific survival — % (95% CI)†				
At 5 yr	99.4 (98.3–99.8)	100	100	
At 10 yr	98.8 (97.4–99.5)	99.0 (97.2–99.6)	99.6 (98.4–99.9)	
Prostate-cancer deaths per 1000 person-yr (95% CI)†	1.5 (0.7–3.0)	0.9 (0.4–2.2)	0.7 (0.3–2.0)	0.48

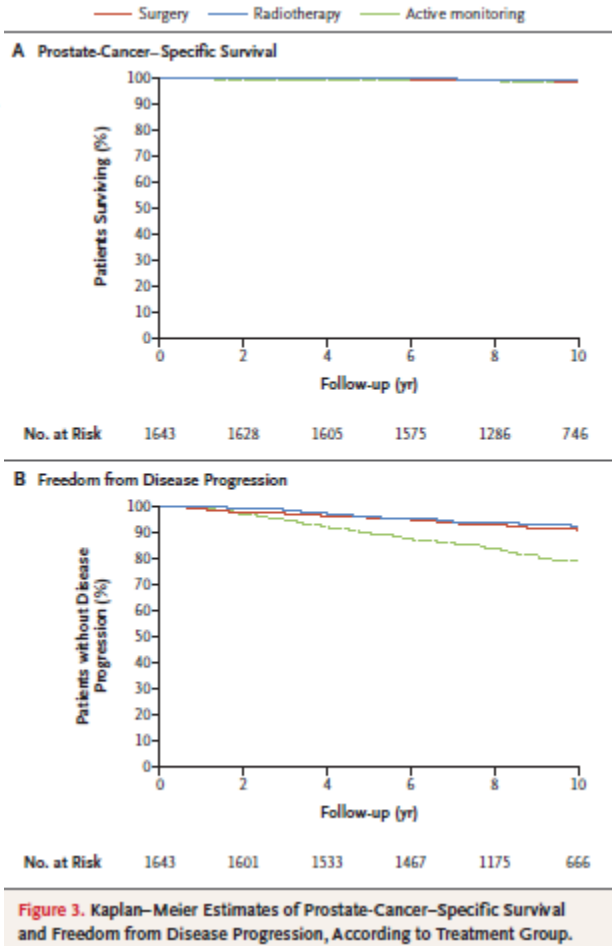


Figure 3. Kaplan–Meier Estimates of Prostate-Cancer–Specific Survival and Freedom from Disease Progression, According to Treatment Group.

Równoważność RP i RT w zakresie CSS i FDP w 10-letniej obserwacji,
Wyższość obydwu metod w stos. do AS

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

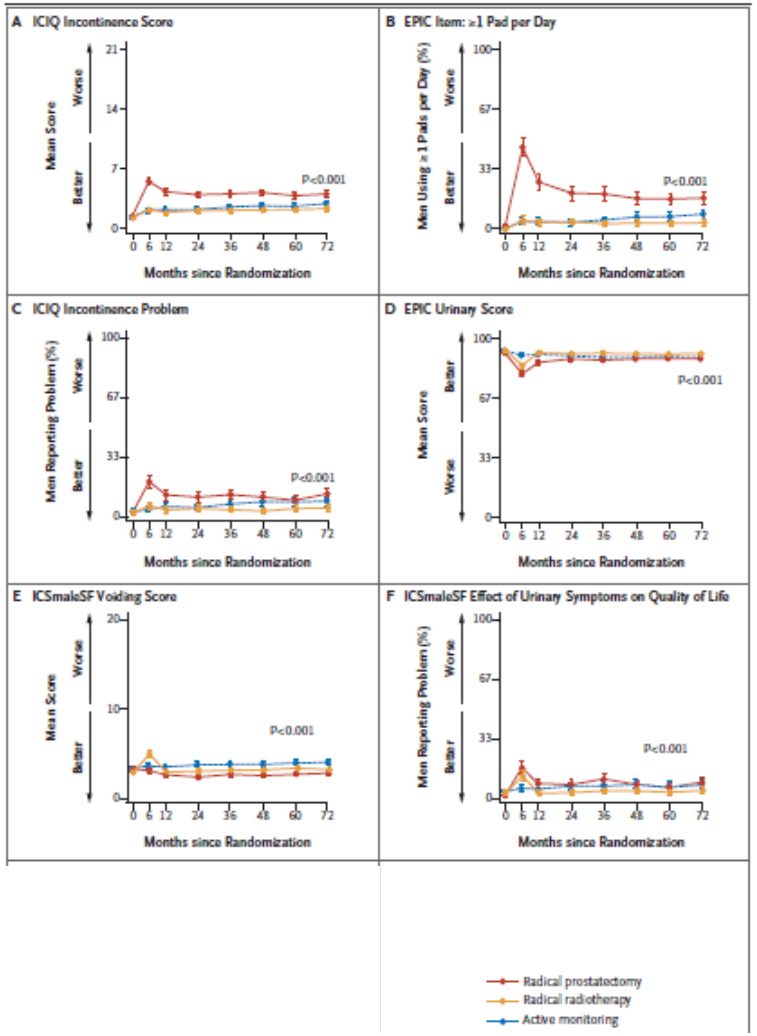
Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer

J.L. Donovan, F.C. Hamdy, J.A. Lane, M. Mason, C. Metcalfe, E. Walsh,

This article was published on September 14, 2016, at NEJM.org.

Preferencja chorych dla RT w stosunku do RP w aspekcie:

kontroli mikcji,
opróżnienia pęcherza moczowego,



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer

J.L. Donovan, F.C. Hamdy, J.A. Lane, M. Mason, C. Metcalfe, E. Walsh,

This article was published on September 14, 2016, at NEJM.org.

Preferencja chorych dla RT w stosunku do RP w aspekcie:

zachowania funkcji seksualnych

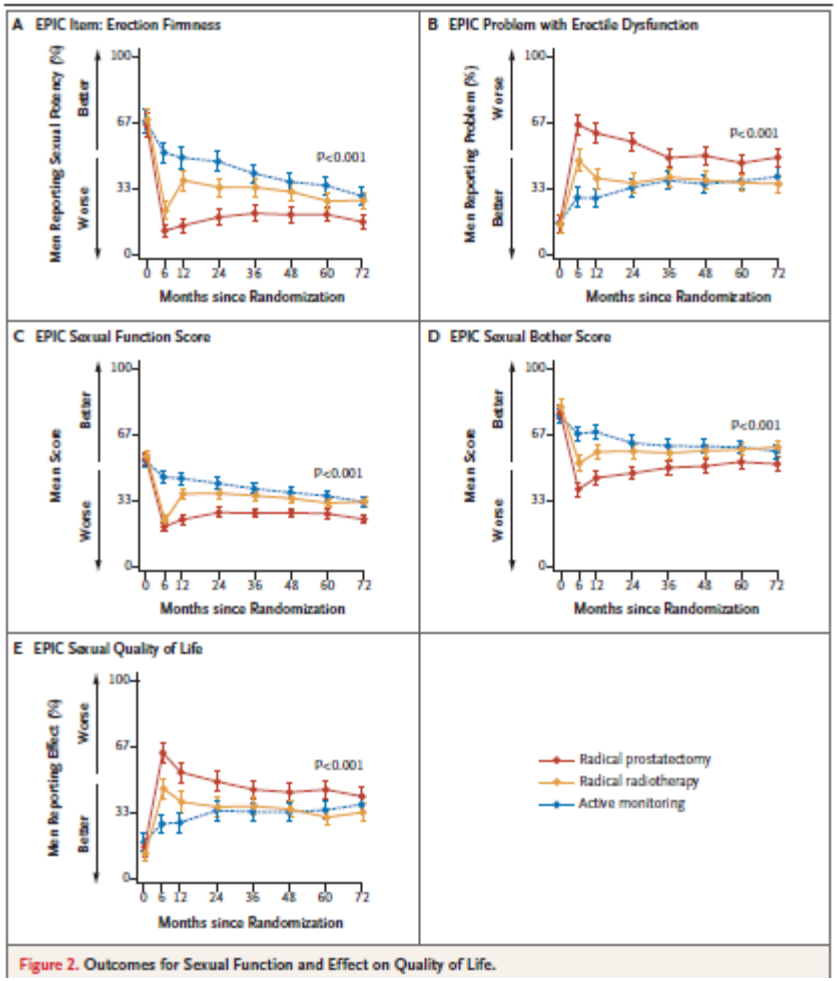


Figure 2. Outcomes for Sexual Function and Effect on Quality of Life.

Podsumowanie dla RT:

- Diagnostyka/planowanie w oparciu o TRUS, TK, RM, PET?
- Nowoczesne techniki IMRT, IGRT, terapia łukowa
- Hipofrakcjonowanie (skrócenie całkowitego czasu leczenia, podwyższenie BED)
- Integracja z brachyterapią
- Preferowana metoda RT w IR – BT lub EBRT+BT (4-6 mies. ADT)
- Preferowana metoda RT w HR i vHR – EBRT+BT (24 mies. ADT)

RP w grupie wysokiego ryzyka progresji (HR) (EAU)

- Kwalifikacja do RP powinna być wynikiem wielospecjalistycznej konsultacji
- RP ma miejsce w leczeniu chorych HR, chociaż jest wciąż przedmiotem kontrowersji !

- cT3 w 13%-27% pT2

  ale… 34-66% SM+, 8-49% pN(+)

- Konieczna wiarygodna diagnostyka przed RP - mpRM miednicy
- Konieczne najwyższe kwalifikacje chirurga

Chory musi być poinformowany o możliwości koniecznego uzupełniającego leczenia (RT/ADT)

Rekomendacja

Każdy chory z grupy podwyższonego ryzyka progresji po RP

powinien być konsultowany przez onkologa-radioterapeutę!!!!

Dziękuję za uwagę!